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COLLECTIVE REVIEW

THIOURACIL AND ITS ALLIES IN THE TREATMENT OF HYPERTHYROIDISM

An Experimental and Clinical Survey

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THE surgical approach designed to control hyperthyroidism has been highly satisfactory in terms of the clinical results obtained. Nevertheless, an adequate medical management is still desirable for those selected patients for whom surgical intervention is for some reason contraindicated, or in whom there remains a persistent hyperthyroidism even after a suitable thyroidectomy. The use of thiouracil and its derivatives has been suggested for such patients. These powerful goitrogenic drugs have also been found of value preoperatively, and particularly in patients in whom the sufficient response to iodine has, at times, been questioned. Since these are problems which often confront the surgeon in this field, an extensive review of the experimental background together with the clinical application of thiouracil and its allies has been made and is here presented.

Chesney, Clawson, and Webster tested the goitrogenic properties of cabbage and other Brassicae in 1928. Later, Marine and his associates (134) noted that the administration of acetonitrile produced thyroid enlargement in rats; iodine, however, prevented this goitrogenic effect. In 1941, the MacKenzies and McCollum, during their study of the effect of sulfaguanidine upon the bacterial synthesis of vitamins in the rat intestine, noted that enlargement of the thyroid gland ensued (131). Richter and Clisby, investigating the effect of bitter tasting substances in rats, found that phenylthiourea induced goiter formation. Kennedy, after studying the Brassicae, suggested that the goitrogenic effect of rapeseed was due to thiourea (112, 113).

In 1943, Astwood and his coworkers adapted a modified thiourea compound, thiouracil, which was found to have powerful metabolism inhibiting qualities (10). After preliminary animal experimentation, Astwood reported clinical improvement of 2 patients with hyperthyroidism following from 1 to 2 weeks of intensive medication with thiouracil (7).

Williams and Bissell subsequently confirmed the clinical applicability of the drug. Since the pioneer reports there have been numerous papers presenting the favorable response of hyperthyroidism to thiouracil (3, 42, 90, 99, 103, 105, 143, 163, 170, 177, 216).

Significant in the early history of thiouracil is the varied response which it received throughout the medical world. At first it was hailed as a panacea which would ultimately displace the surgical management of hyperthyroidism. This enthusiasm, however, was short-lived. The pendulum soon swung and rejection even replaced the early acclaim. The widely recognized toxic effects appeared to outweigh its potential value. With the accumulation of more data there now appears to be a more moderate outlook for some thiouracil-

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like drug, less toxic than thiouracil, in the preoperative preparation of selected patients with hyperthyroidism.

THE METABOLISM AND ACTION OF THIOURACIL

Studies pertaining to the absorption, distribution, metabolism, and excretion of thiouracil are but few. The most comprehensive work to date is that of Williams and his associates (212, 220, 221). These workers report that the drug rapidly disappears from the gastrointestinal tract. It is improbable that all of any given oral dose is absorbed from the digestive tract since gastric juice, the duodenal content, the jejunal content, as well as the staphylococcus aureus and the hemolytic streptococcus are able to inactivate the drug (212, 221). Approximately 15 per cent of the drug given orally is destroyed in the digestive tract (38). Within an hour 50 per cent of a single oral dose is absorbed, while a maximum blood level is obtained within from 15 to 30 minutes. Repeated small doses of 0.2 gram every fourth hour maintain blood levels of from 2.5 to 3.0 milligrams per 100 cubic centimeters. When such amounts are given for 3 days and then stopped, the blood concentration falls abruptly, and the blood is clear of the drug within 48 hours (212, 221). In the blood stream, thiouracil enters both the red and white cells, but the concentration is greatest in the white cells (126, 127, 187, 212, 221). It is present in high concentration in the serum (221).

Studies by Williamson and his associates suggest that thiourea is readily absorbed from wounds (223). These workers have pointed out that many ointments containing sulfonamides, peroxides, and tannic acid also contain thiourea that has been added as an antioxidant. They observed that when 100 milligrams of ointments containing 1 per cent and 10 per cent thiourea were applied weekly to experimental wounds on rats, thyroid hyperplasia and a great diminution in the amount of stored colloid ensued.

Thiouracil enters most organs and body fluids (187). After administration it is present in large quantities in the thyroid, bone marrow, ovaries, liver, and pituitary gland. Smaller amounts have been demonstrated in the kidneys, adrenals, pancreas, brain, heart, lungs, testes, prostate, spleen, and striated muscle. The drug has been found in edema fluid, cerebrospinal fluid, pleural fluid, ascitic fluid, pericardial fluid, urine, and in human milk. The concentration in human milk is 3 times that of whole blood (38, 187, 212, 221). Transfer across the placenta also occurs, and the action of the drug upon the fetal thyroid has been demonstrated (59, 80).

The method or methods involved in the breakdown of thiouracil and its allies in the animal organism are obscure. When thiouracil is incubated with liver tissue, 33 per cent is destroyed within 2 hours (212); however, the amount of inactivation appears to be inversely proportional to the amount of liver tissue present.

The response to a given dose of thyroxine in the rat is greatly intensified after subtotal hepatectomy (111). A similar study to determine the effect of thiouracil after subtotal hepatectomy would be of great interest.

Thiouracil is rapidly excreted in the urine. When 1.0 gram of thiouracil is given orally to a fasting patient, 75 per cent is excreted in 10 hours and 96 per cent within 24 hours (41). The amount of thiouracil excreted as such, however, is uncertain, but probably varies from 39 per cent (38) to 50 per cent (212, 221). Seventy-five per cent of an oral dose of thiourea has been recovered in the urine of the dog (162). When from 0.1 to 0.2 gram of thiouracil (a common preliminary dose) is given to a normal fasting man, urinary excretion is maximal during the second hour and then gradually decreases. However, as the total daily dosage increases, the percentage excreted per day decreases (187, 212). Cystosine and uracil are detectable in the urine of dogs fed thiouracil (187). Additional studies pertaining to the metabolism of the thiouracil-like drugs are necessary before any comprehensive understanding of their absorption, distribution, and excretion can be reached.

The ability of the goitrogenic drugs to cause thyroid hypofunction is now generally recognized. Depression of the basal metabolic rate in rats fed thiouracil has been reported frequently (17, 81, 152, 179, 192). Growth retardation as well as depression of the basal metabolic rate in rats has been reported after promizole (95) and thiouracil feeding (80). Muhrer and Hogan observed abnormal fat deposition and retarded growth in swine fed thiouracil. Inhibition of amphibian development has also been described (84, 85, 187). Thiouracil treated rats are more able to withstand reduced oxygen tensions than are normal animals (81, 86). Lowering of the basal metabolism in hyperthyroid patients has been reported in almost every paper discussing such instances. A few of these reports may be mentioned (19, 22, 24, 28, 52, 58, 66, 75, 87, 90, 104, 142, 154, 164, 165, 166, 167, 189, 211, 217). Myxedema also occurs after thiouracil therapy (3, 32, 143, 151, 170).

Thiouracil induced changes in the thyroid glands of animals and human beings are strikingly similar. The hypertrophied thyroid, increasing in both size and weight, becomes soft, friable, and more

vascular than the normal thyroid. The gland may even become fibrous and nodular. Hyperplasia also occurs. The acinar cells increase in number as well as in size. The lumina of the acini are frequently obliterated by the cellular overgrowth. The nuclei of the cells tend to be centrally located. The picture of tall as well as of low columnar cells, general hyperplasia, lymphoid infiltration, and colloid depletion seen as the result of thiouracil therapy closely resembles the changes frequently seen in uncontrolled exophthalmic goiter. Withdrawal of the drug is usually followed by regression of these findings (21, 75, 92, 140, 149, 181, 196). Similar microscopic appearances have been reported in rats after treatment with promizole (95).

The hyperplasia of the thyroid subsequent to thiouracil treatment appears to be due to secondary stimulation of the thyroid by an increased amount of circulating thyroid stimulating hormone elaborated by the anterior pituitary lobe. Thus hypophysectomy prevents the thyroid hypertrophy and hyperplasia normally seen after the administration of promizole (96) as well as other goitrogenic drugs (10, 187). Simultaneous administration of whole pituitary extract and goitrogenic drugs to hypophysectomized animals causes little if any stimulation of the thyroid. Resultant hyperplasia of the thyroid is greater in the normal animal when thyroid stimulating hormone and thiouracil are given simultaneously than when either is given separately (187). Griesbach, Kennedy, and Purves (88) attribute the development of thyroid adenomas in rats fed seeds of the Brassicae to stimulation by thyroid stimulating hormone.

Gordon, Goldsmith, and Charipper (84) have noted that an increase in the circulating thyroid stimulating hormone, similar to that noted after subtotal thyroidectomy, is not detectable in the thiouracil treated animal. They conclude, consequently, that the thyroid is largely responsible for the removal of thyroid stimulating hormone from the blood stream. In addition, they have reported that the hyperplastic, thiouracil treated gland has an increased avidity for thyroid stimulating hormone since they found the circulating thyroid stimulating hormone was strikingly and suddenly increased when the goitrous glands were removed. That the circulating thyroid stimulating hormone is increased, and that the hyperplastic gland has an avidity for it are also suggested by the work of Larson *et al.* (118). These investigators noted that the thyroids of chicks treated with thiouracil have a decreased ability to "trap" radioactive iodine. However, when thiouracil was withdrawn, they observed that the ability of the glands to "trap" radioiodine was greatly enhanced and even approached that of normal thyroids stimulated by thyroid stimulating hormone. The work of Barker (17) again suggests that thyroid stimulating hormone is capable of stimulating the thiouracil treated thyroid gland. He reports a further increase in the size of the glands of thiouracil treated rats and that such rats respond metabolically to thyroid stimulating hormone even though such responses are greatly decreased when compared to those of normal rats. It has also been observed that the pituitaries of rats fed thiouracil present the same picture as do the pituitaries of thyroidectomized rats (10, 129, 130).

Although thiouracil collects in relatively large quantities in the anterior pituitary lobe (38, 187, 212), no reports of a direct stimulatory action of the drug upon the *pars distalis* have been found in the literature surveyed.

Most investigators now agree that the principal action of the thiouracil-like drugs is to prevent the formation of thyroid hormone. This is suggested by the depletion of the colloid in the glands of thiouracil treated animals. Colloid reappears when the drug is withdrawn. The profoundly decreased metabolic response to thyroid stimulating hormone exhibited by thiouracil treated rats (17) is further evidence that thyroid hormone formation is greatly diminished. However, the response of thiouracil treated rats to the administration of thyroid substance is within normal limits (16). Thiouracil treated rats respond to thyroid feeding, but the response is too irregular to permit the use of such animals for the bioassay of thyroid substance (152).

The amount of thyroxine required to inhibit the production of thyroid stimulating hormone is unchanged by thiouracil therapy (89). Approximately 4.8 micrograms of thyroxine per day are required to restore to normal the metabolic rates and thyroid glands of rats previously given 0.1 per cent thiouracil in their drinking water for 2 weeks (179). Thyroxine or desiccated thyroid given with promizole completely inhibits its goitrogenic properties (95). Small doses of desiccated thyroid administered with thiourea to patients prevented an increase in size of the goiters so treated (58). The increase in the serum globulin that occurs during thiouracil therapy, as well as in hypothyroid states, can be prevented or reversed by the administration of thyroid substance (120, 121). Since thyroxine or thyroid substance can prevent the goitrogenic action of the thiouracil-like drugs, it is in all probability true that these goitrogens do not interfere with the utilization of the thyroid hormone once it is formed (94, 132).

Barker (15) has made the interesting observation that thiouracil treated rats do not respond metabolically to dinitrocresol as do normal rats. He suggested that either the thyroid hormone must be present before a metabolic response to dinitrocresol is secured or that dinitrocresol acts through the thyroid cells.

The simultaneous administration of iodine with the thiouracil-like drugs does not prevent their goitrogenic action (92, 187, 192). Larson and his associates (118, 119) have reported that the ability of the chick's thyroid to take up radioactive iodine is greatly decreased within 1 hour of the administration of thiouracil. Chagas, De Robertis, and Couceiro find that the amount of iodine in the thyroid follicle is decreased by thiourea. The alveolar colloid produced under the influence of the goitrogenic drugs is poor in iodine (7, 72, 98, 178). The thyroidal iodine of rats is severely depleted by administering 150 milligrams of thiouracil per day in food containing 13 micrograms of iodine (192). Thiouracil has been shown to interfere with the incorporation of iodine into thyroxine and diiodotyrosine both in vitro and in vivo (71, 73, 187). The exact point at which the formation of thyroglobulin is checked has not been established (178). In patients treated with thiouracil, the thyroidal organic and inorganic iodine content diminish, the circulating protein-bound iodine decreases and the total blood iodine concentration decreases. The urinary iodine excretion first rises and then falls as the body is depleted of iodine. From evidence such as this, it has been concluded that the thiouracil-like drugs prevent the synthesis of the thyroid hormone by the thyroid gland.

That the thiouracil-like goitrogens interfere with some cellular oxidation mechanism is strongly suggested by the work of De Robertis and Goncalves (61). These authors have ascertained the normal oxidation-reduction potential of normal thyroid cells and colloid to be +0.050 and −0.200 volts, respectively. Stimulation with thyroid stimulating hormone increases the potential of the colloid to the same level as that of the cells. These authors have also noted that the administration of thiourea both in vivo and in vitro reduces the oxidation-reduction potential of the cells and colloid of thyroid stimulating hormone stimulated thyroids to −0.200 volts. In addition, the goitrogenic activity of sulfonamide compounds depends upon the presence in the molecule of a free aromatic amino group or a free aromatic hydroxyl group, both of which are easily oxidized (203). Carboxyl and sulfonamide radicals bear but little relation to antithyroid activity. Astwood, Bissel and Hughes (9) have studied 220 goitrogenic compounds and have observed that the 2 types of chemical structure associated with antithyroid activity are (1) the thiocarbonamide group, and (2) the aminobenzene group. These, too, are easily oxidizable. The chemical structure of the sulfonamides differs greatly from that of the thiouracils and it is probable that the site as well as the mechanism of thyroid inhibition is different (2).

As yet the exact mechanisms by which the thiouracil-like drugs inhibit the formation of thyroid hormone are uncertain. The main hypotheses maintain that the drugs inhibit some enzyme system or systems responsible for the formation or iodination of thyroid protein, or that the drugs themselves combine with iodine in such a way that it is no longer available to the cells of the thyroid.

It is probable that more than one enzyme system is involved in the complicated process of forming the thyroid hormone. The cytochrome oxidase and peroxidase systems were perhaps the first to be implicated (60). Thiouracil was shown to be capable of inhibiting peroxidase (187). Schachner, Franklin, and Chaikoff have reported that the in vitro formation of thyroxine and diiodotyrosine is inhibited by KCN, hydrogen sulfide, cobalt, and NaN_3. Since only 2 enzyme systems, the cytochrome oxidase and the polyphenol oxidase, are inhibited by all of these inhibitor substances, and since polyphenol oxidase is not present in the thyroid, these investigators concluded that the cytochrome oxidase system was intimately related to the in vitro formation of the thyroid hormone. Paschkis and his coworkers (169, 171) were able to demonstrate that cytochrome oxidase activity of the thyroid in vitro could be decreased 51±6.3 per cent by 0.002 molar solutions of thiouracil, but could not inhibit the activity of this enzyme in kidney slices and in bone marrow where it is of the same magnitude as in the thyroid. They also reported that the cytochrome oxidase activity of the thyroid glands of rats fed 0.05 per cent thiouracil in their drinking water for 2 weeks was subnormal. However, Lerner and Chaikoff were not able to inhibit cytochrome oxidase activity with thiouracil. Thiouracil has been found readily to inhibit the in vitro formation of melanin by the enzyme tyrosinase (168), but it exerts no inhibitory action upon xanthine oxidase or triosephosphate dehydrogenase (187). Since the goitrogenic activity of the cyanide compounds can be prevented by the administration of iodine, while that of the thiouracil-like compounds cannot (185), it appears that these 2

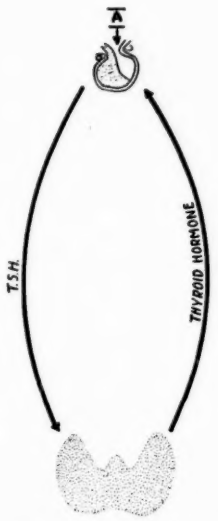

Fig. 1. The normal reciprocal relationship between the anterior pituitary lobe and the thyroid gland. Thyrotropin appears to govern the formation and release of the thyroid hormone. The thyroid iodine is normally 2 milligrams per gram of dried gland. The total blood iodine is 4.2 ± 1.2 micrograms per cent. The acetone-insoluble blood iodine is 0.9 ± 0.2 micrograms per cent. The urinary iodine depends upon the intake as well as the geographic region.

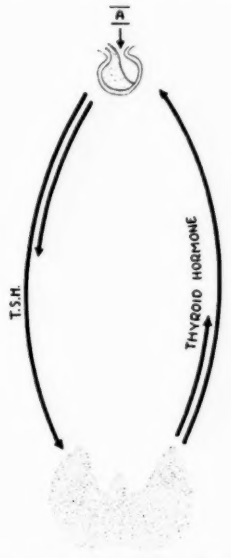

Fig. 2. Graves' disease—untreated. The normal reciprocal relationship between the anterior pituitary lobe and the thyroid gland is broken by some unknown mechanism. Thyrotropin appears to accelerate thyroid hormone formation and its release into the circulatory system. The thyroid iodine is diminished (0.2 milligram per gram of dried gland). The total blood iodine and the protein bound blood iodine are increased. The urinary iodine is increased.

goitrogenic groups may interrupt the formation of thyroid hormone at different stages (194).

Campbell and Landgrebe reported that thiourea has a striking affinity for iodine. On the basis of the reaction:

$$2\ C\ S\ N_2H_4 + I_2 \rightleftharpoons C_2SN_4H_2H\ I$$

they state that 1.4 milligrams of thiourea will combine with 1.63 milligrams of iodine. The reaction is reversible if the concentration of thiourea is above 0.04 per cent. Such a reaction could readily occur when the blood concentration of thiourea is at therapeutic levels. Similar reactions can probably occur with other easily oxidizable goitrogens. This becomes more significant when one considers that the total blood iodine normally averages about 230 micrograms. Salter, Cortell, and McKay (192) have recently reported that thyroid protein continues to be formed by the thiouracil-treated thyroid gland. This would favor the hypothesis that the goitrogenic drugs compete with the thyroid cells for iodine. However, if the thiouracil-like drugs block only the iodination of the thyroid protein and do not affect the metabolism of desiodothyroglobulin, they are remarkably specific. Extensive further studies are necessary before the exact action of the thiouracil-like drugs upon the thyroid cell will be definitely known.

Figure 1 presents diagrammatically the normal anterior pituitary-thyroid relationship. This appears to be governed by some unknown factor "A"; corticothalamic mechanisms may play a role. This aspect of the physiologic relation between the thyroid and anterior pituitary lobe is but poorly understood. There is recent evidence that thyroid stimulating hormone is intimately related to the storage and release of thyroid hormone from the follicles (62, 63, 110, 118, 209).

Figure 2 presents the pathologic physiology of untreated Graves' disease. The normal reciprocal relationship of the anterior pituitary lobe and thyroid is presumably broken by the action of some unknown mechanism. As a result the anterior pituitary lobe is stimulated to produce increased thyroid stimulating hormone. Under these circumstances the thyroid is greatly stimulated and manufactures increased amounts of hormone, yet apparently cannot manufacture

enough to inhibit the production of thyrotropin. The unknown mechanism stimulating the anterior pituitary lobe appears stronger than the greatly increased circulating thyroid hormone. Thyroidal iodine decreases as the circulating protein-bound iodine rises, and as this occurs the urinary excretion of iodine increases. The patient then goes into a negative iodine balance, unless sufficient supplemental iodine is given.

Figure 3 presents diagrammatically the action of iodine in Graves' disease. The increased iodine does not appear to alter the fundamental pathologic physiology of Graves' disease, yet it does correct the negative iodine balance. The theory regarding the mode of action of the administered iodine is still controversial, but it is probable that this action prevents the increased release of thyroid hormone into the circulation (63) for a variable period of time. Clinically, this is evidenced by the induced "iodine remission" from active Graves' disease. Iodine therapy greatly increases the thyroidal iodine, decreases the circulating protein-bound iodine, and results in great storage of iodine (54).

Figure 4 presents diagrammatically the effects of treating Graves' disease with thiouracil. The fundamental pathologic physiology remains. As thiouracil is given, the production of thyroid hormone diminishes and eventually ceases. The anterior pituitary lobe thus loses this stimulation with a resultant production of increased thyroid stimulating hormone. Subsequently the thyroid gland becomes even more hyperplastic. Since the ability of the thyroid to take up iodine is greatly diminished by the action of thiouracil, the thyroidal iodine, already decreased by the disease, is further decreased. The circulating protein-bound and inorganic iodine decrease as the urinary iodine first rises and then falls as the organism, already greatly depleted of iodine, is still further depleted.

THE TOXICITY OF THIOURACIL

Toxic reactions, directly attributable to the use of thiouracil, have been reported in from 6.7 per cent (21) to 18 per cent (75) of the cases of hyperthyroidism so treated. The percentage of toxic reactions which may be expected in patients treated with thiouracil is approximately 13.1 as reported by Van Winkle and his associates who analyzed 5,745 cases collected from various clinics. Similar figures of 14.4 (138), 12 (142), and 14.5 per cent (218) have been reported.

Reports of toxic reactions due to simple overdosage are few. However, reports of toxicity due to idiosyncrasy are increasing at a rapid pace (12, 13, 68, 77, 78, 124, 135, 155, 173, 197, 205, 214, 225). Hypersensitivity reactions are the most dangerous. Most feared is the depression of the bone marrow resulting in diminution of the leucocytes and particularly of the granulocytes.

Various writers have presented different criteria as to what constitutes leucopenia and granulocytopenia. This has made evaluation of the available data difficult. It is suggested that Van Winkle's definitions of leucopenia and granulocytopenia be generally adopted in order to avoid confusion in the further evaluation of goitrogenic drugs. Leucopenia (225) is defined as that state in which the leucocytes number 4,000 or less, and the differential count is normal, while the patient presents no subjective symptoms. Similarly, granulocytopenia is defined as that state in which the white blood cells number 4,000 or less, while the differential count reveals a particular decrease in the granulocytes (225). Others, however, have thought that once the differential count shows a decrease in the granulocytes, the diagnosis of granulocytopenia should be made and the drug stopped before the clinical signs of fever, malaise, and pharyngitis become evident. If Van Winkle's criteria were to be generally adopted and all cases so reported, it would appear that the incidence of granulocytopenia induced by thiouracil should increase.

Resultant leucopenia, neutropenia, granulocytopenia, and agranulocytosis are commonly reported. These reactions vary in degree from a slight shift to the left in the entire leucocytic series, that returns to normal even if the drug is not discontinued (124, 216), to severe and even fatal agranulocytosis (68, 122, 155, 173, 197). Many reactions varying between these two extremes have been observed (19, 21, 22, 52, 74, 75, 117, 130, 139, 142, 143, 164, 165, 174, 177, 178, 181, 201, 217, 218, 224).

A leucopenia existing before thiouracil therapy may even disappear during treatment (143), or the drug may convert it into a severe agranulocytosis (218).

Leucopenia has an over-all incidence of approximately 4 per cent (155, 225). According to Van Winkle it accounts for 30 per cent of all toxic reactions, and 23 per cent of the patients with this condition develop agranulocytosis. Gabrilove, Kert, and Soffer (75) report that 9 of 51 patients had a depression of the white cells and of these, 6 developed agranulocytosis. Agranulocytosis has been reported after as little as 7 days of treatment (205), after a year of continuous treatment (218), and 6 months after the treatment was stopped (225). The most frequent time for agranulocytosis to develop is between the fourth and eighth weeks

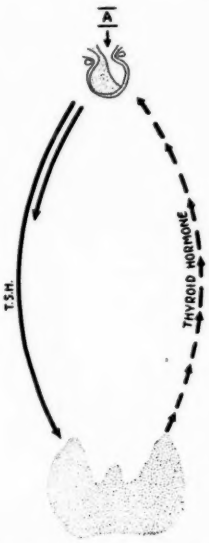

Fig. 3. Graves' disease—iodine treated. The normal reciprocal relationship between the anterior pituitary lobe and the thyroid gland is broken by some unknown mechanism. The inorganic thyroid iodine and the organic thyroid iodine are increased. The inorganic blood iodine is increased, but the protein-bound blood iodine is decreased, even to normal limits. The urinary iodine is greatly increased. The iodine probably acts in some way to block the release of the thyroid hormone from the gland, but the block is temporary.

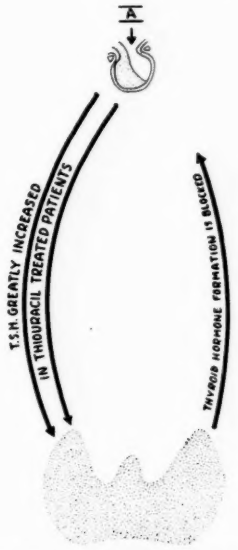

Fig. 4. Graves' disease—thiouracil treated. The relationship between the anterior pituitary lobe and the thyroid gland is further interrupted as the formation of thyroid hormone is blocked. The thyroid gland becomes hyperplastic and the thyroid iodine greatly decreases. The total blood iodine and the protein bound blood iodine decrease. The urinary iodine first increases and then diminishes.

of treatment (142, 218). It is generally agreed that dosage bears little or no relation to the time of the onset of agranulocytosis. Moore (155) and Van Winkle and his associates (225), after exhaustive surveys, report an incidence of 1.74 per cent and 2.5 per cent, respectively, in patients treated with thiouracil. Fishberg and Vorzimmer (70) have reported an incidence of 20 per cent. An incidence of 14 per cent was noted in our series of 35 collected cases.

Since thiouracil concentrates in the bone marrow (38, 167, 187, 210) to a greater degree than in the serum of patients receiving the drug (212), it is probable that in some way it interferes with the bone marrow metabolism with a resultant granulocytic depression. Limarzi and associates (126) have induced a severe neutropenic leucopenia in a patient suffering from myeloid leukemia by administering thiouracil. Vogel and McGavack have produced mild anemia and definite myeloid depression by feeding rats from 0.1 to 0.2 gram of thiouracil per day, and have stated that in the rat bone marrow is a more reliable index to agranulocytosis than is the peripheral blood. Agranulocytosis may be detectable in the blood, hours before the clinical symptoms develop (19).

Warren has produced myeloid hyperplasia of the bone marrow of rats with intrapleural injections of croton oil. He observed that thiouracil produced definite depression of the respiration in the myeloid series as measured by the Warburg apparatus. However, Paschkis and his associates (169) were unable to inhibit the cytochrome oxidase activity of bone marrow in vitro in 0.002 and 0.01 molar solutions of thiouracil. Concentrations of 0.01 molar thiourea were equally ineffective in this respect. To date no studies on bone marrow respiration have been reported after either man or animal has developed severe agranulocytosis induced by thiouracil. The exact mechanism by which the bone marrow is depressed is as yet unknown, but the resultant bone marrow hypoplasia and toxic agranulocytosis have been frequently observed (1, 4, 14, 19, 20, 75, 124, 143, 205). Bone marrow studies during life are few (127).

The high concentration of thiouracil in the leucocytes (38, 126, 127, 187, 210) suggests that mature cells may also be subject to toxic action.

However, we have found no studies pertaining to the duration of life of the granulocytes of patients treated with thiouracil. Thiouracil may affect the release of granulocytes from the bone marrow as well as their maturation (127).

Repeated frequent observations of the patient as well as of his blood cells have been advocated by almost every writer who has reported a series of cases of hyperthyroidism treated with thiouracil. Even this has not prevented the development of agranulocytosis. Once it develops, all agree that the drug should be immediately withdrawn and steps taken to stimulate the bone marrow and to ward off infection. An ensuing infection may precipitate a thyroid crisis (205). Penicillin appears to be the best agent available for combating infection and its use has been recommended (218), as has the simultaneous use of whole blood transfusions (190). Because of the known ability of the sulfonamide drugs to produce idiosyncratic reactions and depression of the bone marrow, it is suggested that they be used in the treatment of thiouracil induced agranulocytosis only when the superimposed infection is resistant to penicillin therapy. The use of pyridoxine hydrochloride (43, 70, 140) and of pentosenucleotide has been reported (135).

The administration of liver and folic acid simultaneously with thiouracil, in order to prevent the development of agranulocytosis, has been commented upon both favorably (124) and unfavorably (218), as has the concurrent use of liver alone with the thiouracil-like drugs (125, 136). Daft and his associates gave the L. casei factor to rats and noted minimal protection against the development of agranulocytosis when thiouracil was given. Thyroxine was also ineffective. Palmer (167) has reported that cevitamic acid counteracts the effect of thiouracil upon the bone marrow. Lahey and associates (117) advocate the combined use of penicillin, pyridoxine, and folic acid in the treatment of agranulocytosis. This feared toxic reaction with a reported fatality rate varying from 14 per cent (155) to 26 per cent (225), and even 50 per cent (117) certainly demands the best treatment in our therapeutic armamentarium. Limarzi and Ricewasser (127), however, have emphasized that the key to recovery is not primarily the treatment directed against the agranulocytosis, but rather the amount of bone marrow damage that has occurred. They have advocated that bone marrow studies be made as an index of prognosis.

Mild, transient anemia has also been observed in rats fed thiouracil (55, 208, 210); nevertheless, bone marrow studies reveal little or no depression of the erythroid series. Warren, who produced erythroid hyperplasia of the bone marrow by intraperitoneal injections of acetylphenylhydrazine has reported that the respiration of young erythrocytes is relatively unaffected by thiouracil. One report of severe thiouracil induced anemia in 2 patients receiving the drug was found in the literature reviewed (142).

Deaths have been reported by various authors (27, 52, 68, 75, 77, 100, 109, 124, 155, 225, 226). Cope, speaking before the American Association for the Study of Goiter on June 22, 1946, placed the number of deaths due to thiouracil at 27. We can add 1 more.

Other severe reactions due to idiosyncrasy are drug fever (1, 4, 74, 141) and dermatitis (74, 137, 143, 198). Drug fever has an over-all incidence of 2.7 per cent and dermatitis occurs in approximately 3.3 per cent of the patients treated with thiouracil (225). Drug fever with a sudden increase in temperature usually develops after from 10 to 18 days of treatment (138). The temperature falls to normal when the drug is stopped and is most apt to rise again if small amounts of the drug are subsequently given. Purpura (66, 218), maculopapular rashes, macular rashes, urticaria, pruritis and scleroderma (117) have been reported following the use of thiouracil. Both drug fever and dermatitis indicate sensitization of the patient and demand that the thiouracil be stopped lest further reaction occur. It appears probable that thiouracil combines in some way with the protein of the blood (218), and that antibodies against this combination are formed. This is a likely basis for the sensitivity reactions that are reported.

Myxedema is also one of the complications resulting from continued thiouracil therapy (3, 143, 170), but is reversible when the drug is withdrawn. Administration of thiouracil to rats from the time of birth results in retardation of growth, arrested development, mild anemia, and changes similar to those seen in cretinism (102).

Swelling of the submaxillary glands is a frequent development in patients receiving thiouracil (52, 77, 117, 164, 201, 217, 218). Nussey (164) has also reported enlargement of the parotid glands. Williams and associates (218) have reported general lymphadenopathy. That the adenitis, almost specific for the salivary glands, is an idiosyncratic reaction is suggested by the occurrence of the Mikulicz syndrome in a case reported by Bishop and Rawson. This patient developed fever and swelling of the salivary and lacrimal glands. Bacterial cultures were negative, and there was no response to chemotherapy while thiouracil was given. The condition improved remarkably within 48 hours after the drug was stopped. Recurrence was

abruptly precipitated within 3 hours when a small dose of the drug was again given. Shrinkage of the spleen in experimental animals to one-half, or even to one-fourth, of its normal size has been reported by Baumann and Marine (25). Meuther and Anderson (149) reported an enlarged thymus which they attributed to thiouracil treatment.

Waller and Charipper established normal values for the electrocardiogram of the rat, and then studied the changes induced by thyroidectomy and thiourea treatment. These workers noted an increase in conduction time in thiourea treated animals and a decrease in the conduction time in thyroidectomized animals. Both thyroidectomized and thiourea treated animals showed a decrease in heart rate, but this was more pronounced in the thiourea treated rats in which the rate decreased to two-thirds of the normal, i.e., the rate decrease paralleled the increase in conduction time noted. The thyroidectomized animals showed a decrease in the voltage of the R waves and a decreased total amplitude of the QRS complex, while the thiourea treated animals showed the reverse. Both groups showed a decrease in the amplitude of the T waves, but this was greater in the thiourea treated group.

Rose and McConnell observed a gradual decrease in the cardiac output of patients receiving the drug. Bain reported the case of a patient with hyperthyroidism treated with thiouracil in whom fever, profound bradycardia, complete atrioventricular disassociation, pericarditis, and slight jaundice developed. These alarming developments subsided when the drug was stopped. The complete heart block reported by Bain becomes more significant when considered in the light of the greatly increased conduction time reported by Waller and Charipper.

The development of the lesions of periarteritis nodosa has been reported in both man and animals given thiouracil. Marine and Baumann (133) noted the development of these lesions in rats fed thiouracil for 23, 312, and 365 days. The lesions developed along the path of absorption of the drug from the gut. Such hypersensitivity may be induced by specific thiouracil protein conjugates formed in the gut, or their hydrolytic products which are then absorbed through the lymphatics. Gibson and Quinlan (78) reported the case of a hyperthyroid woman who received 31.5 grams of thiouracil in 35 days. She first complained of joint pain and numbness of the extremities. Jaundice, leucoderma, and conjunctivitis then developed. The vibratory sense and ankle jerks were lost, and coma and death supervened. Autopsy revealed panarteritis characterized by intense fibrinoid degeneration and perivascular cuffs of inflammatory cells. The arteritis was most evident in the liver, spleen, thyroid, adrenals, kidney, and heart.

Similarly Rich (185) reported the case of a patient with thyrotoxicosis treated with Lugol's solution who suddenly developed fever. Potassium iodide was then administered and the patient developed a high fever, skin rash, joint pains, lymphadenopathy, and splenomegaly. Autopsy revealed periarteritis nodosa lesions in the liver, spleen, pancreas, kidneys, testes, and prostate. Hypersensitivity to iodine has long been known, yet idiosyncratic reactions to iodine are rare in hyperthyroid patients.

Raab has used thiouracil in the treatment of angina pectoris on the same basis that total thyroidectomy was formerly done for selected patients with the anginal syndrome. Thyroidectomy decreases the amount of circulating thyroid hormone and thus diminishes the sensitivity of the heart to epinephrine. Experimentally, a greater amount of epinephrine than usual is required to cause cardiac death in rats treated with thiouracil, and conversely a decreased amount of epinephrine is required to cause death in thyroxine treated rats (181) (187). However, thiouracil administration also increases the production of adrenotropic hormone by the anterior pituitary lobe (187). The mechanism responsible for this effect is as yet obscure. Raab reported that 8 of 10 patients so treated were benefited. Ben-Asher has noted good results in 7 of 8 patients treated, but his best result was in a patient with an associated basal metabolic rate of plus 24 per cent.

Purpuric reactions (66, 218) have been noted. They may be due to an increase in capillary permeability, or to a decrease in the number of thrombocytes. The latter has been reported (19).

Basophilic hyperplasia and eosinophilic hypoplasia of the anterior pituitary lobe, similar to that subsequent to thyroidectomy, are induced by thiouracil and other goitrogenic drugs (89, 96, 187, 192). The production of the gonadotropic and adrenotropic hormones is increased (120, 187).

Liver damage caused by thiouracil has been reported to vary from a slight jaundice to acute yellow atrophy. Jaundice (13, 19, 52, 77, 151, 198, 201, 205, 217), toxic hepatitis (147, 150) and acute yellow atrophy (188) have all been observed. Meuther and Anderson have noted jaundice clinically, with central necrosis and peripheral degeneration of the hepatic lobules at necropsy (149). However, their observations are difficult to evaluate, since their patient died in a postoperative crisis. The mechanism of liver damage by thiouracil is obscure. The cholinesterase activity of liver slices treated with thiouracil is twice normal, yet

the in vitro respiration of liver slices is normal (187). In view of the reports of liver damage, caution is advised when giving thiouracil to hyperthyroid patients who already show liver damage as evidenced by diminished liver function tests.

Baumann and Marine (25, 26) reported extensive observations pertaining to the effect of thiouracil upon the adrenal cortex of the rat. They noted that a reduction of the cortex to half of the normal size occurs by the third or fourth month of treatment. All 3 layers of the cortex were decreased in size. Dalton and associates have made similar observations. Atrophy of the human adrenal cortex after death from thiouracil has been reported (149). However, no changes of the oxygen uptake of the adrenal slices occur in vitro, and the blood chemistry changes of adrenal cortical disease do not develop (187). It has been stated by Baumann and Marine that recovery of the cortex later occurs even if the drug is continued. An infection resulted in cortical enlargement in the presence of an atrophy previously induced by thiouracil. The relation of an increased amount of adrenotropic hormone (187) to these changes is not clear. In vitro concentrations of thiourea as low as 6×10^{3} to 10^{3} molar inhibit the stimulatory effect of from 2 to 10 micrograms of epinephrine per liter of glucose tyrode bath on the gut and rabbit uterus. The addition of plasma or red blood cells to the tyrode bath prevents this inhibition. However, doses of from 10 to 200 milligrams have no effect upon the autonomic mechanisms of the intact rat (64, 187).

Thiourea appears in mother's milk and also passes the placental barrier (80, 102, 197). Goldsmith, Gordon and Charipper (80) have given pregnant rats 0.5 per cent thiourea in drinking water for from 1 to 15 days before parturition. They observed that hyperplasia of the fetal thyroid and retarded growth were transient. However, the 15 day period of treatment was probably too short to deplete the maternal thyroids of thyroid hormone. These same observers (85) have noted that thiourea inhibits the metamorphosis of Rana pipiens larvae and also inhibits the stimulatory effect of thyroid stimulating hormone upon the larvae.

Chu has reported that thyroid hormone is necessary for normal gestation in the rabbit, and has demonstrated that embryos of thyroidectomized rabbits are resorbed or aborted, and that the administration of thyroid substance permits normal gestation and parturition to occur.

Davis and Forbes have reported the sudden death of a 21 year old woman during the sixth month of gestation. She had been treated with thiouracil before and throughout pregnancy, and was on a maintenance dose of 200 milligrams daily. No sensitivity was mentioned. The lobes of the fetal thyroid were hyperplastic and showed no evidence of colloid storage. Williams (214) observed no ill effects in 3 infants whose mothers had received thiouracil during the period of gestation.

Thiouracil has been advocated as a measure to control hyperthyroidism during pregnancy (25, 27, 31, 34, 132, 166, 176, 214). However, controlled experiments in which the effects of thiouracil given to animals and human beings during pregnancy were studied are too few. Until such experiences are reported and evaluated, the advisability of prolonged thiouracil treatment during pregnancy remains questionable.

Goldsmith and Harnly (83) have noted that concentrations of from 10 to 12.5 milligrams of thiourea per 100 cubic centimeters of water are strikingly lethal for the larvae of the ebony, black, and sooty mutants of Drosophila melanogaster. Fifteen milligrams per 100 cubic centimeters produce 100 per cent mortality of the wild larvae. Goldsmith and Harnly even suggested the use of thiourea as an insecticide!

Deposition of thiouracil in the urinary tract of experimental animals has been reported (25, 207). McGavack and Vogel (144) found renal calculi in rats given 5-methyl and 5,6-dimethylthiouracil. Barr and Shorr (19), Astwood (1), and Williams *et al.* (218) have reported hematuria in patients receiving thiouracil. Paschkis and his associates (171) observed that the cytochrome oxidase activity of kidney slices in vitro is not depressed by 0.002 and 0.01 molar concentrations of thiouracil.

Varied disturbances of the central nervous system during thiouracil therapy have been noted. Atkin observed delusional psychoses. Leys reported euphoria after methyl thiouracil, and Hammer has noted somnolence and mental confusion following thiouracil. Delusions and a persecution complex exhibited by a patient receiving the drug were studied by Pearson. Cessation of the drug ameliorated the symptoms, and further dosage precipitated the same psychosis. Loss of the vibratory sense, loss of the ankle jerks, and then coma were observed in 1 patient by Gibson and Quinlan. Haines and Keating, and Hammer have reported myoclonic muscular contractions and muscular twitchings. Cannon observed improvement in anxiety states after thiouracil therapy, but the improvement was greatest when there was an associated elevation of the basal metabolic rate. Riker and Wescoe citing the work of Ellis and Root state that the cholinesterase activity of brain slices taken from rats that had received thiouracil is within normal limits. The altered physiology responsible for these central nervous system symp-

toms is obscure. No studies of the brain metabolism in animals receiving the drug were found in the literature reviewed.

Unobserved and less apparent dangers of the thiouracil-like drugs are suggested by Bielschowsky, who produced cancer of the thyroid gland in rats with the combined medication of 2-acetylaminofluorene and allylthiourea (31). 2-Acetylaminofluorene is a carcinogen which heretofore has not been known to affect the thyroid gland; yet when used in combination with allylthiourea, which alone produced hyperplasia of the thyroid follicle cells, cancer results. Purves and Griesbach have reported the development of carcinoma of the thyroid in 2 of 30 rats after prolonged treatment with thiourea. Metastases were found in the thyroid veins and also in the lungs. These authors attribute the malignancy to prolonged stimulation of the thyroid cells by thyrotropin. These reports again raise certain doubts as to the clinical applicability of the thiourea compounds, particularly in patients with nodular goiter in whom the threat of malignancy is already present in varying degrees.

Many reports discussing the various toxic responses are available (19, 21, 53, 75, 77, 87, 142, 155, 164, 174, 201, 211, 218, 219, 225).

A classified list of toxic responses gleaned from the literature follows:

TOXIC RESPONSES

Bone Marrow Effects
1. Agranulocytosis
2. Anemia
3. Granulocytopenia
4. Leucopenia
5. Neutropenia
6. Thrombocytopenia

Cardiovascular Effects
1. Heart block
2. ECG changes
3. Periarteritis nodosa
4. Pericarditis
5. Purpura
6. Flushing

Central Nervous System Effects
1. Coma
2. Confusion states
3. Delusions
4. Dizziness
5. Headache
6. Loss of ankle jerks
7. Loss of vibratory sense
8. Nausea
9. Vomiting
10. Persecution complexes
11. Various psychoses

Gastrointestinal Effects
1. Nausea
2. Vomiting
3. Diarrhea
4. Abdominal pain

Liver Effects
1. Acute yellow atrophy
2. Degeneration of hepatic lobules
3. Hepatitis
4. Jaundice

Lymphatic Effects
1. Enlarged lymph nodes
2. Enlarged salivary glands
3. Leg edema
4. Myxedema
5. Decreased size of spleen
6. Enlargement of thymus

Miscellaneous Effects
1. Arthritis
2. Choking
3. Dryness of the mouth
4. Faintness
5. Hematuria
6. Fever
7. Joint pains
8. Muscular pains
9. Pharyngitis
10. Thirst

Ophthalmic Effects
1. Chemosis
2. Conjunctivitis
3. Decreased exophthalmos
4. Increased exophthalmos
5. Photophobia

Effects upon the Skin
1. Leukoderma
2. Macular rashes
3. Maculopapular rashes
4. Morbiliform rashes
5. Purpura
6. Pruritus
7. Urticaria
8. Urticaria with pruritus
9. Painful subcutaneous swellings
10. Scleroderma

CLINICAL EVALUATION

Many experienced observers have carefully studied the clinical applications of thiouracil. Additional papers confirming its ability to decrease the basal metabolic rate are available (18, 37, 38, 53, 56, 65, 67, 69, 77, 79, 92, 108, 122, 140, 152, 158, 159, 160, 161, 165, 181, 183, 184). Leiter *et al.* determined the effect of thiouracil upon the hyperthyroidism resultant from functioning metastases of thyroid carcinoma. In one of their patients the cervical thyroid tissue had been radically extirpated. Activity of the metastases in this, as well as in another patient, was demonstrated by radioiodine studies. The administration of thiouracil caused a decrease in the basal metabolic rate, and an increase in the blood cholesterol and in the body weight. The urinary excretion of radioactive iodine was doubled during thiouracil therapy. Recurrence of the hyperthyroidism occurred when the drug was withdrawn. No effect upon the growth of the metastases was reported.

Iodine administration previous to thiouracil therapy causes a slower response to the drug (19, 92, 151, 167, 187, 214, 217), but does not prevent its characteristic goitrogenic action (58).

Some depletion of the thyroid hormone already manufactured and stored appears to occur before its action becomes evident clinically, since thiouracil, soon after its administration, decreases the ability of the thyroid to take up iodine (119).

Initially, 0.6 grams in 3 divided doses of 0.2 gram each are usually given daily until the basal metabolic rate has fallen to normal limits. Then maintenance doses of from 0.1 to 0.2 gram per day are continued (21, 22, 29, 33, 53, 56, 69, 101, 117, 151, 155, 211, 217, 225). Therapeutic blood levels on dosages such as this vary from 1 to 6 milligrams per 100 cubic centimeters. One day of treatment is usually required for each percental elevation of the basal metabolic rate (21, 117). However, there is usually an initial lag period varying from 2 to 3 weeks before the basal metabolic rate falls toward normal (52, 75). Six weeks of treatment may be required before the basal metabolic rate becomes normal (217). However, the response to the drug is slower if the disease has been of long duration (87). A basal metabolic rate

that is high initially may fall rapidly during thiouracil therapy, while a low one may fall quite slowly (174). The basal metabolic rate also falls more rapidly in young people (211). Early hyperthyroidism responds more rapidly than chronic. The hyperthyroidism of diffuse hyperplastic goiter responds more favorably than does that of toxic nodular goiter (29, 167, 183, 187). In a relatively small number of patients there is no response to the drug (51, 52, 66, 147, 187, 189). Poate failed to secure a remission of the hyperthyroidism caused by a functioning fetal adenoma, with thiouracil therapy.

Other changes in addition to the decreased basal metabolic rate also indicate a reduction in metabolic activity. The blood cholesterol rises (21, 52, 141, 142, 148, 211), and there is a more or less straight line relationship between the elevation of the blood cholesterol and the falling basal metabolic rate (141). It has also been observed that the blood cholesterol may rise to myxedematous levels before the basal metabolic rate decreases to similar levels (16). The protein bound iodine of the blood decreases to normal (117) and its fall may be more rapid than that of the basal metabolic rate (211, 214). These findings we are able to confirm. The excretion of calcium, nitrogen, phosphorus, and creatinine is decreased toward normal limits (19). An increase in the plasma or serum globulin occurs even though the total blood protein may remain unaltered (120, 121). An increase in the plasma chloride and a decrease in the plasma carbon dioxide combining power have also been reported (93). The effects of thiouracil upon the blood magnesium partitions are controversial (35).

Exophthalmos is generally unaffected by thiouracil administration (66, 69, 139, 187). McGavack *et al.* (142) noted no increase of exophthalmos in 38 patients with Graves' disease treated with thiouracil. Decreased lid spasm and increased body weight may give the illusion of a decrease in exophthalmos (187). However, untoward reactions varying from slight ocular irritation with conjunctivitis and lacrimation (167) to an increase in exophthalmos (19) have been reported (187). Periorbital edema associated with high cholesterolemia has been reported during thiouracil therapy (147). Thyroid substance has been given to prevent untoward ocular reactions (167, 161, 187). Additional accurate exophthalmometric measurements are required before the relation of thiouracil to exophthalmos can be accurately assessed.

Thyroid enlargement, noted subsequent to the feeding of the Brassicae to animals, led to the discovery of the goitrogenic drugs. However, there is as yet little agreement as to how much the human thyroid enlarges or regresses during thiouracil therapy. Apparently the degree of enlargement is not related either to dosage or duration of the treatment (21, 66). Great enlargement, accompanied by a striking increase in vascularity (140), as well as 20 per cent (62) and from 30 to 40 per cent decreases (53) in the size of the thyroid have been observed. Initial enlargement followed by transient decreases after 2 or 3 weeks of therapy have also been reported (142). Watson made measurements of the necks of 35 patients who received the drug and stated that the increase in the size of the neck varied from 0.25 to 1.0 inch and averaged 0.63 inches. Water restriction does not prevent thyroid enlargement in rats given thiouracil (208). The increase in the size of the gland as well as other evidences of goitrogenicity may be prevented by the administration of thyroid substance (58, 89, 95).

Thyroid enlargement induced by thiouracil becomes of major significance when the pre-existing goiter is substernal, retrovisceral, or retrovasal. Severe pressure symptoms due to an enlarging substernal goiter have been reported (206). The tendency for older nodular goiters to undergo vascular degeneration with repeated hemorrhages, together with the ability of thiouracil to cause an increase in the vascularity of the goiter should also be considered, whether the goiter is substernal, retrovasal, or simply cervical.

Patients treated with thiouracil often state that they feel better before there is any obvious clinical improvement (142). Tremor, agitation, and perspiration are usually improved before tachycardia is decreased (69). Tachycardia decreases more slowly than the basal metabolic rate (69) and is usually the last sign of hyperthyrodism to abate (99, 187).

A relatively high per cent of remissions of long duration subsequent to thiouracil therapy has not been observed. The ability of any similar drug to maintain decreased thyroid function after its withdrawal would appear to be limited unless it actually destroyed thyroid cells. There are no satisfactory criteria by which to judge the duration of treatment with thiouracil and to determine which patients are most apt to have remissions (139). Six months of treatment before withdrawal of the drug has been advised (6, 204). However, McGavack *et al.* (142) have continued treatment as long as 16 months. Williams (214) states that if the initial basal metabolic rate is relatively low and the thyroid relatively small, remissions are more apt to occur than if the initial basal metabolic rate is high and the gland large. He also writes that remissions are more frequent in those pa-

tients in whom the size of the thyroid gland decreases during therapy. Males are more apt to relapse than females. Treatment for less than 6 weeks is usually followed by a relapse within 2 weeks after withdrawal of the drug; treatment for 6 weeks or more usually results in remissions lasting longer than 2 months (29). Relapses are less frequent if treatment is continued for 2 months or longer and are also most apt to occur within 2 months of the withdrawal of the drug (29, 214). After thiourea therapy, remissions are more prolonged if small amounts of thyroid are given simultaneously (58).

Various periods of remission after thiouracil therapy have been observed. Remissions varying from 3 to 21 months (214), from 2.5 to 7 months (142), from 2 to 11 months (66), from 2 to 15 months (69), from 3 to 7 months (189), and from 8 to 12 months (217) have been reported. Most observers agree that the number of patients followed for a long period after withdrawal of the drug is as yet too small to permit general conclusions (29). Salter and his associates (192) have attributed remissions to a "thiouracil hangover" effect upon the thyroid cells. However, there is at present no way of determining how long this effect will continue when the drug is discontinued after any given regimen of dosage.

Beierwaltes and Sturgis have re-emphasized the cyclic nature of Graves' disease and have cited Plummer's earlier work which points out that the disease may fluctuate with remissions and exacerbations for from 2 to 4 years before a true remission occurs. It would seem that similar periods should elapse before it could be maintained that a relatively permanent remission was induced by thiouracil.

The cyclic variation of hyperthyroidism makes the evaluation of remissions difficult (191). The many relapses that occur provide good evidence that the effect of the drug may be quite transient once it is withdrawn. There is also evidence that thyroid function may return to, and even exceed, the normal when administration of the drug is stopped (119, 139).

Diabetes mellitus complicated by hyperthyroidism is benefited by the reduction in metabolism induced by thiouracil as it is by the usual iodine therapy. Reveno (184) noted that the diabetes mellitus was less severe in 7 of 19 collected cases. A decrease in the insulin requirement of 2 such patients was noted by Fishberg and Vorzimmer (69).

The use of thiouracil as an adjunct to the existing means of preoperative preparation of hyperthyroid patients has been advocated by many (21, 22, 27, 56, 101, 117, 128, 140, 151, 152, 188, 191, 195, 200, 204, 217). It appears probable that the drug or its allies will find their proper place in the preparation of those patients for surgery who would be very poor risks indeed if prepared by other ordinary methods alone. Here thiouracil should be used as a supplement to the other methods (195) and not as a single therapeutic agent (27).

Many surgeons have noticed that the thiouracil induced hypervascularity often causes a persistent oozing that is difficult to control during surgery. Because of this Bartels (21, 22) advocated the administration of iodine before surgery to cause involution of the hyperplastic gland. This method of preoperative preparation has been most widely adopted and is briefly as follows: —0.6 grams of thiouracil are given daily until the basal metabolic rate approaches plus 20 per cent and then iodine is administered simultaneously. However, thiouracil is withdrawn about 1 week before surgery and iodine is then given alone. Operation is not advised until the basal metabolic rate is normal and the improvement in symptoms has been maximal (21, 22, 56, 116, 117). Ten milligrams of iodine per day have been found adequate to induce involution in such patients (140). The course during and after surgery has been reported to be more smooth than when thiouracil was used alone (117, 217). Lahey and associates (117) write that this preoperative regimen has all but eliminated 2 stage thyroidectomies, and has greatly reduced the mortality among bad risk patients. Montague and Wilson (224) have written that thiouracil will probably find its greatest use in the preoperative preparation of thyrotoxic patients, unless the induced remissions can be maintained for several years after withdrawal of the drug.

King and Rosellini reported that 8 of 10 patients with acute thyroiditis, all of whom received thiouracil within 3 weeks of the onset of the disease, were very much benefited within 1 week. These patients were given 0.6 gram of the drug daily in 3 divided doses, and a subsequent decrease in the body temperature and tenderness of the gland were noted. Two patients that had previously received iodine did not respond. At present there is no understanding as to why the thiouracil therapy was beneficial. The hyperplasia ordinarily induced by thiouracil and its tendency to result in hypothyroidism are effects that must be carefully evaluated when the drug is given to treat a disease that also tends toward the development of thyroid hypofunction. Additional studies are required before the rationale of thiouracil therapy for such patients can be established.

OTHER GOITROGENS

Thiourea was one of the first goitrogens to be studied extensively (41, 55, 58, 78, 80, 81, 86, 120, 121, 187). Clinically, the drug is given in doses of from 1 to 3 grams daily. Its use was discarded because of a relatively high incidence of toxic reactions. Danowski and his associates have recently reinvestigated its clinical use and have reported that much smaller doses than were given previously are effective. The serum precipitable iodine was also decreased by such a regimen. These authors have also advised the simultaneous use of small amounts of iodine and desiccated thyroid.

Astwood and his associates have studied the antithyroid activity of thiobarbital (5, 7). Thirty patients were treated and a relatively high incidence of drug fever was observed. Death from agranulocytosis occurred in 1 patient. The drug was given in doses of from 0.2 to 0.3 gram daily. However, it is excreted slowly, a factor which may account for the increased incidence of toxicity. Bartels (23) has reported toxic reactions in 28 per cent of a series of 28 patients treated with thiobarbital.

Leys treated 19 cases of hyperthyroidism with methyl thiouracil by giving 0.8 gram daily until the basal metabolic rate approached normal limits. Then maintenance doses varying from 50 to 200 milligrams daily were administered. A period of from 10 days to 6 weeks elapsed before the antithyroid action of the drug became evident. Euphoria, eosinophilia, and leucopenia frequently occurred. Drug fever following methyl thiouracil has been reported (206, 224).

Williams (213) observed the effects of tetramethylthiourea. In rats goitrogenic activity develops within 14 days, when their drinking water contains 0.04 per cent of the substance. The drug is excreted slowly and relatively high blood concentrations are obtainable. Thirty patients with hyperthyroidism were also treated. Decreases in the basal metabolic rate and blood protein bound iodine were observed, as was also the development of leucopenia and urticaria. Diethylthiourea was administered to 4 patients and the toxic effects were noted in each.

Paraxanthine has been reported to have antithyroid properties (187). However, Williams (213) found that it has no effect upon the metamorphosis of Rana catesbiana tadpoles. Likewise, it fails to prevent the increase in oxygen uptake of liver slices such as occurs when these are treated with thyroglobulin. A patient with Graves' disease received huge doses of paraxanthine for 11 days and was not benefited. These findings have been confirmed by Barker (15), who gave from 50 to 10,000 micrograms per kilo per day to rats and noted no depressant effect upon the basal metabolism.

Para-aminobenzoic acid decreased the oxygen consumption of rats from 25 to 35 per cent after their drinking water contained 3 per cent for 3 weeks. No toxic symptoms were noted (86).

Higgins (95, 96, 97) has studied the goitrogenic activity of promizole in the rat and has noted depression of the basal metabolic rate and hyperplasia of the thyroid. This substance is approximately 18 per cent as active as thiouracil (146).

The effects upon rats of 6-methylthiouracil; 5, 6-dimethylthiouracil; and 2-thio, 4,5-dimethyl-6-methylethylpyrimidine have been studied by McGavack and Vogel (144). These 3 substances are extremely toxic and have a great tendency to cause renal and liver damage. McGinty and Bywater have studied many thiourea derivatives (145), imidazoles (40), and sulfones (146). Pyridine-2-thiol, thiazoline-2-thiol, and benzimidazole-2-thiol have goitrogenic properties. Sulfides corresponding to sulfones are more active than the sulfones. Thiourea derivatives have also been extensively studied by Christenson (47). No goitrogenic properties are exhibited by 1, 7-dimethyl guanine (15).

Ethyl and also propyl thiouracil have been used both experimentally (8) and clinically (11) by Astwood and his associates. In man, propyl thiouracil is approximately 5 times as effective as thiouracil, and also more active than ethyl thiouracil. The initial dose of propyl thiouracil given to patients was 75 milligrams per day and this was followed by maintenance doses of from 25 to 50 milligrams daily. Propyl thiouracil is now under extensive trial in this and other clinics. Of all the goitrogens thus far studied, it appears the most promising. In 29 patients treated with 6-N-propyl thiouracil, no toxic effects were noted (11).

DISCUSSION AND SUMMARY

Following Astwood's initial announcement of the use of thiouracil in the treatment of hyperthyroidism, the thiouracil-like drugs have been widely studied. After 3 years of extensive clinical investigation, certain facts pertaining to their use are generally recognized. The drugs are rapidly absorbed from the gastrointestinal tract, and repeated small doses maintain satisfactory blood concentrations. They enter most of the body fluids and tissues, particularly the thyroid, the blood, the bone marrow, and the leucocytes. Transfer across the placenta also occurs and their goitrogenic action has been demonstrated in the fetal thyroid. Drugs of this type appear to be metabolized in the liver and excreted in the urine.

The thiouracil-like drugs block the formation of thyroid hormone, yet the exact mechanism by which this is accomplished remains obscure. The diminution of thyroid hormone formation with the ensuing drop in the blood concentration stimulates the anterior pituitary lobe to produce more T.S.H. which in turn induces further hyperplasia of the thyroid cells. Moreover, the thyroid gland of the organism treated with the thiouracil-like drugs is unable to respond to the usual pituitary stimulation. A drop in the basal metabolism consequently ensues. Approximately 1 day of medication is required for each percental elevation of the basal metabolic rate of the hyperthyroid patient. Depression of thyroid function to myxedematous levels may occur. The blood cholesterol, creatinine, and proteins return to normal levels as the metabolism decreases toward normal limits. These goitrogenic drugs further deplete the hyperthyroid organism of iodine which is excreted largely in the urine.

The effects of the thiouracil derivatives on exophthalmos are controversial, but an increase in exophthalmos can and does occur during therapy as exemplified by one of our patients. Caution is advised when patients with severe exophthalmos are considered for such therapy. Enlargement of the thyroid and an increase in vascularity occur during therapy with the thiouracil derivatives. This becomes of significance in nodular goiters which may also present hemorrhage or malignancy.

Iodine medication following thiouracil treatment has been successfully used to decrease the hypervascularity of the glands of patients prepared for surgery with the goitrogens. It has been reported that the operative and postoperative courses of patients prepared with thiouracil are much more quiet than those of patients prepared in the usual way. It has also been reported that the need for 2 stage thyroidectomies has been greatly decreased by the use of thiouracil preoperatively.

CONCLUSIONS

After an extensive survey of the experimental as well as of the clinical literature, including a study of the findings of the patients in our clinic, the following conclusions pertaining to the use of the thiouracil-like drugs seem reasonably warranted:

1. The drugs are capable of causing severe toxic symptoms, and should not be used unless accurate observations can be made frequently, preferably under hospital conditions.

2. The incidence of leucocytic depression is higher than is generally recognized since the criteria used have varied. In the majority of cases careful bone marrow studies have not been made. The depression of the circulating leucocytes has thus far been interpreted to be due to depression of the bone marrow elements responsible for their production, rather than to any effect (as yet undemonstrated) upon the mature leucocytes per se. The development of agranulocytosis is detectable in the bone marrow hours before it is shown by a drop in the circulating leucocytes, and, similarly, the decrease in circulating leucocytes will occur before clinical symptoms develop.

3. Toxic reactions also occur during the treatment of hyperthyroid patients with propyl thiouracil.

4. The presence of nodular goiter should make one hesitant regarding the employment of thiouracil-like drugs.

5. The drugs appear to be contraindicated by the following:

a. Hypersensitivity
   (1). Previous history of multiple allergies to foods, drugs (27, 166), and to foreign proteins.
   (2). Previous history of sensitivity to the sulfonamide drugs (27). Simultaneous sulfonamide therapy appears inadvisable.
   (3). Previous history of toxic reaction to one of the thiouracil-like drugs.

b. Bone marrow conditions
   (1). Pre-existing low initial white counts. This would be a contraindication since the patients would appear to possess less reserve if the drug were to depress the granulocytes.
   (2). Pre-existing blood dyscrasias due to bone marrow hypoplasia.
   (3). The presence of an infection demands that the leucocyte response be optimal, and few will risk the unpredictable development of agranulocytosis in such cases (27, 32, 34).

c. Exophthalmos, if severe, appears to contraindicate the use of the drugs (27, 34).

d. Adolescence: long continued treatment does not appear advisable at this time.

e. Toxic nodular goiter: long continued treatment is inadvisable if this condition exists. The threat of malignancy developing in such goiters is well recognized. The functioning fetal adenoma falls into the same category (50, 128, 174).

f. Pre-existing liver disease.
g. Pre-existing adrenal disease. The work of Baumann and Marine (25, 26) suggests that thiouracil might cause additional tissue damage.
h. Pre-existing renal disease, particularly if the renal sufficiency is questioned (166).
i. Pregnancy. Carefully controlled studies on the experimental animal and in man are not yet available to judge the effects of such long continued therapy accurately on either the mother or the fetus. Widespread use of the drug during the period of gestation should be avoided until further studies are available unless the emergency is dire (27, 34).
j. Large cervical goiter (27), retrosternal goiter (206), retrosternal and retrovasal goiter, and retrovisceral goiter, as pressure symptoms may result in these conditions.

6. Indications for the use of the drugs appear to be found within that group of patients in whom the risk of thiouracil therapy is less than the risk of the disease when other methods of control are used, i.e., patients presenting:

a. Refractoriness to iodine (34).
b. Hypersensitivity to iodine (185).
c. Recurrent hyperthyroidism after previous thyroidectomy (34, 151, 187, 195).
d. Recurrent hyperthyroidism with hypertension.
e. Ordinarily bad risks (21, 22, 56, 116, 117) (for preoperative preparation).
   (1). Thyrocardiacs (115).
   (2). Thyrocachectics (187).
f. Hyperthyroidism, and patients who for one reason or another cannot have surgery.

The use of thiouracil alone in the long continued management of hyperthyroidism is now severely questioned. Poate writes that "Early reports have given too optimistic an impression as to the value of the 'thio drugs.' The history of thiouracil is already unpleasantly overloaded with claims for success which have had to be modified subsequently on account of toxic manifestations." McCullagh and his associates (140) state that the "risk of the drug (thiouracil) superimposed on the risk of the disease exceeds the mortality rate with treatment with iodine and competent surgery." Surgery (22) appears to remain the treatment of choice in the management of the majority of patients with hyperthyroidism.

Our own experience further emphasizes the advantages of the well established preoperative management of patients with hyperthyroidism. This consists of sufficient rest; adequate sedation; a high caloric, high vitamin diet; calcium, phosphorus, and vitamin D; and iodinization. This customary regimen reduces the period of preoperative therapy and hospitalization to a minimum. Moreover, it eliminates the time, expense, and technical assistance necessary for repeated leucocyte counts. The hypermetabolism resultant to the hyperthyroidism is sufficiently controlled in the great majority of patients without superimposing the risk of the thio drugs upon the risk of the disease, in order to permit adequate surgery. Since 1943, when thiouracil was introduced, 335 patients have been prepared for surgery in our clinic in the manner briefly outlined with a subsequent operative mortality of 0.29 per cent.

Remissions subsequent to adequate thyroidectomy are more certain and longer lasting than are those yet secured by treatment with the thiouracil-like drugs. It is our opinion that the now well established preoperative management of patients with hyperthyroidism followed by competent surgery will remain the treatment of choice until an antithyroid drug which will have a risk less than that of the disease itself is synthesized. Surgery thus remains the treatment of choice in the management of the great majority of patients with hyperthyroidism.

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ABSTRACTS OF CURRENT LITERATURE

SURGERY OF THE HEAD AND NECK

HEAD

Cavernous Sinus Thrombosis. Samuel L. Fox and G. Brooks West, Jr. *J. Am. M. Ass.*, 1947, 134: 1452.

The term "cavernous sinus thrombosis" is used to include phlebitis, thrombophlebitis and phlebothrombosis, as well as true aseptic thrombosis. By far the majority of reported cases are of septic origin and would therefore be classified as phlebitic or thrombophlebitic. Aseptic thrombosis and phlebothrombosis are usually secondary to trauma, a failing circulation, or to other noninfectious inflammation of the cavernous sinus. Although thrombosis of the cavernous sinus is usually unilateral in its clinical manifestations, there is almost always bilateral involvement histopathologically because of the anatomic communications between the two cavernous sinuses by way of the anterior and posterior basilar sinuses, situated on the floor of the sella turcica under the pituitary body.

There are two primary types of thrombosis of the cavernous sinus: aseptic thrombosis and septic thrombosis. The septic type of thrombosis is by far the commonest, is of infectious origin, and is secondary to a focus elsewhere. The onset is usually manifested by a severe chill, a high temperature ranging from 102 to 105 degrees F., extreme toxicity, and perhaps nausea and vomiting. There is headache, but the patient is mentally alert until meningeal involvement occurs. The first localizing sign is definite edema of the bulbar conjunctiva and chemosis of the eyelids, with rapidly progressive exophthalmos of the eye on the affected side, usually becoming bilateral unless the disease is arrested or the patient dies. There is also limitation of movement of the eye (abducens or sixth nerve paralysis), with concomitant alterations in sizes of the two pupils. Meningitis usually occurs rather early, after which the sensorium is decidedly affected.

The two commonest conditions which must be differentiated from thrombosis of the cavernous sinus are orbital cellulitis and lateral sinus thrombosis.

Prior to the introduction of the sulfonamide drugs as therapeutic agents, the treatment of thrombosis of the cavernous sinus was most unsatisfactory and the prognosis was extremely grave, whether medical management or surgical intervention was employed.

The prognosis is still grave in spite of advances in the use of chemotherapy, anticoagulants, and antibiotic agents. The treatment of thrombosis of the cavernous sinus is purely medical, and surgical intervention is only indicated at the site of origin of the infection to eradicate the focus. The combined use of sulfonamide compounds, antibiotics (penicillin, streptomycin, and others) and anticoagulants in large doses is strongly advised. If the case is unresponsive to one of the sulfonamide drugs another should be substituted and the same is probably true of the antibiotic agents. The early employment of heparin and dicumarol, administered simultaneously, also is advocated.

Three cases of cavernous sinus thrombosis are reported (2 with unilateral involvement and 1 with bilateral involvement), with two recoveries. In the first case the condition was unilateral and was thought to have followed adenotonsillectomy. In the second case the condition followed dental extraction with probable secondary sinusitis, and was complicated by meningitis. In the third case it was believed to have occurred following a gumma of the nasal septum with secondary infection in a person with uncontrolled diabetes.

STEPHEN A. ZIEMAN, M.D.

EYE

Specific Treatment of Ocular Burns Due to Lewisite (β-Chlorovinyldichloroarsine). Irving H. Leopold and Francis Heed Adler. *Arch. Ophth.*, Chic., 1947, 38: 174.

The authors present information on the specific treatment of ocular burns resulting from lewisite (β-chlorovinyldichloroarsine). An effective antiarsenical agent, BAL (2, 3-dimercaptopropanol), was discovered and developed during the war years which also proved effective against various types of arsenical poisonings in civilian practice.

The value of BAL for the treatment of burns of the eye is summarized as follows:

BAL is superior to hydrogen peroxide and potassium permanganate, which were previously used as therapeutic agents for this condition.

The longer the interval before the application of BAL to an eye burned by lewisite, the lower the effectiveness of the treatment. The effectiveness decreases rapidly after from 10 to 12 minutes, but some effect is still present even after 30 minutes. The use of BAL an hour after contamination has no beneficial effect.

Better therapeutic results are obtained by reapplying the drug after the initial application.

Although unstable, watery solutions yielded the best therapeutic results. More stable solutions can be made with ethylene glycol or propylene glycol. These solutions retain full therapeutic efficiency for considerable periods of time under temperatures and exposures to air most likely to be encountered in practice.

Although preservatives do not reduce the therapeutic efficiency of BAL there is no necessity for their employment.

BAL also has been found to be therapeutically effective in ointment bases.

Several drops of 3 and 5 per cent solutions of BAL are just as effective as those of a 10 per cent solution.

BAL has a specific effect not only on ocular lesions resulting from lewisite but also on those from methyldichloroarsine, ethyldichloroarsenine and phenyldichloroarsine, and when used immediately after contamination of the eyes it has a beneficial effect on lesions due to mustard gas.

JOSHUA ZUCKERMAN, M.D.

Penetration of Locally Applied BAL into the Anterior Chamber of the Rabbit Eye. Irving H. Leopold and Willard H. Steele. *Arch. Ophth.*, Chic., 1947, 38: 192.

The authors discuss the penetrability of BAL into the anterior chamber of the rabbit's eye. They conclude that after local application, solutions of BAL in water and in ethylene glycol penetrate through the cornea into the anterior chamber. Penetration from a water vehicle is more rapid than that from an ethylene glycol vehicle. However, aqueous solutions of BAL are unstable.

BAL penetrates more readily from a water containing base (K-Y jelly) than from a nonaqueous base (Friedenwald-Fuqua ointment).

Greater penetration into the aqueous humor occurs from application of a 5 per cent solution of BAL in water than from application of a 5 per cent solution in ethylene glycol. JOSHUA ZUCKERMAN, M.D.

Gonorrheal Iritis: Experimental Production in the Rabbit. Maurice J. Drell, C. Phillip Miller, and Marjorie Bohnhoff. *Arch. Ophth.*, Chic., 1947, 38: 221.

Experimental iritis was produced in the eyes of rabbits, preferably albinos, by the injection of 0.2 c.c. of a saline suspension of two strains of gonococci into the anterior chamber, with withdrawal of a like amount of aqueous. That it was a true infection was manifested by the multiplication of organisms and their recovery on culture. Inoculation with various numbers of organisms indicated 200 organisms to be the minimal infecting dose. The appearance of the experimental infection was similar to that frequently seen in such cases in the human eye. There was a gelatinous exudate, intense engorgement of the iris, and hypopyon and hyphemia. The infection remained localized in the anterior part of the eye.

The percentage of eyes yielding cultures containing the gonococcus fell progressively during the first week after inoculation. Injury to the lens at the time of the inoculation had a tendency, it seemed, to make the infection chronic.

In vivo testing of gonococcidal agents was carried out. Details of this work are not related in the present paper; however, it is mentioned that although huge doses of penicillin systematically administered were necessary to control the infection, as little as 2.5 units of penicillin injected directly into the anterior chamber were efficacious.

It is noted that an exact diagnosis of gonorrheal iritis can rarely be made in man. Paracentesis of the anterior chamber is not ordinarily feasible; furthermore it was found that aspiration of aqueous frequently yielded no culture whereas postmortem culture of the tissues sometimes revealed a heavy growth of the organisms. The present knowledge of the immunological reactions in gonorrhea is not extremely helpful in establishing it as the etiologic factor in cases of acute iritis and the diagnosis of gonorrheal iritis must usually be presumptive.

WILLIAM A. MANN, M.D.

Central Pulverulent (Discoid) Cataract and Its Hereditary Transmission. Andrew Rados. *Arch. Ophth.*, Chic., 1947, 38: 57.

The author analyzes a hereditary form of cataract, variously known as "Coppocks cataract" (from the name of the family in whom it was first extensively reported), discoid cataract (Doyne) or central pulverulent cataract (Vogt), on the basis of a study of the family trees of patients whose cases have been reported. It is believed that the mode of inheritance is dominant. Evidence is presented to refute the idea of the recessive nature of the inheritance.

WILLIAM A. MANN, M.D.

Substitution of Spinal Fluid for Vitreous. Milo H. Fritz. *Am. J. Ophth.*, 1947, 30: 979.

The author presents an historical account in which he describes the previous attempts to clear vitreous opacities by the substitution of normal saline and vitreous for the clouded vitreous. Following the suggestion of Hegner, who in 1929 used cerebrospinal fluid for this purpose, the author reports 4 cases in which cerebrospinal fluid was substituted for vitreous.

In only one case was the effort highly successful. A 13-year-old boy whose vision was reduced to light perception as a result of a traumatic hemorrhage showed a visual acuity of 20/20-1 in a period of 1 year after the procedure. Since the surgery was not performed until 12 months after the injury, it is unlikely that spontaneous improvement would have occurred. The other 3 patients, all of whom were in the late fifties, tolerated the procedure but did not obtain a satisfactory improvement in vision. This may have been due in one case to a previous retinal detachment and in the other cases to retinal damage from retinitis proliferans following repeated spontaneous hemorrhages.

The method followed was to perform a spinal tap on the patient in bed transferring the sterile cerebrospinal fluid (4 c.c.) to the operating room. A quadrant of sclera was then exposed by making a conjunctival flap, and a purse-string suture was placed at the puncture site about 12 mm. from the limbus. An 18 gauge needle is plunged into the vitreous and as much cloudy vitreous is extracted as can be

readily obtained, this usually being 1 to 1½ c.c. The globe collapses but assumes its normal condition when a similar amount of cerebrospinal fluid is injected. Examination with the ophthalmoscope in the successful case showed an immediate clear channel from the posterior lens capsule to the posterior pole, which enlarged subsequently.

This field, in which there is at present much interest, may in the future offer some hope in otherwise desperate cases. WILLIAM A. MANN, M.D.

EAR

A Study of the Eustachian Tubes and Their Orifices and Lumens in Patients with Large Operative Defects Giving Direct Visualization. Further Studies of the Muscles of Phonation and Deglutition. W. Likely Simpson and Jones E. Witcher. *Ann. Otol. Rhinol.*, 1947, 56: 357.

Studies were made by direct visualization of the palate, nasopharynx, and regions of the eustachian tubes in 5 patients with large operative defects. The movements of the soft palate, uvula, eustachian tube, and lateral walls of the pharynx in pronouncing the vowels and consonants are the same except for degree. The soft palate and uvula are drawn upward. The lateral walls of the pharynx are drawn upward, backward, and toward the midline. The eustachian tube mouth is drawn backward and downward, but there is no tendency for the tubes to close. Yawning produces a similar prolonged movement of these parts. In swallowing there is first a minor movement of elevation of the soft palate and medial displacement of the pharyngeal wall, then a major movement consisting of an upward movement of the posterior one-third of the soft palate and uvula, and depression of the remainder of the palate, followed by an upward movement of the entire soft palate and lateral pharyngeal wall. There is hermetic closure of the nasopharynx from the hypopharynx during deglutition. The normal eustachian tube is open at all times and is not closed or occluded by voluntary movements. JOHN R. LINDSAY, M.D.

Chronic Purulent Otitis Media. M. M. Cullom. *Arch. Otolar.*, Chic., 1947, 46: 137.

The first point which the author makes is the widespread incidence of chronic running ear. There are about 2,800,000 cases in the United States, and the author believes that the responsibility for cure in these cases rests solely with the otologists.

In the great majority of cases, chronic purulent otitis media is believed to be dependent upon chronic purulent sinusitis on the same side as the purulent media, and usually radical surgical drainage of the chronic purulent sinusitis will clear up the chronic purulent otitis media in a dramatic way and in a short time.

A detailed report is given of 5 cases, all with associated purulent sinus disease, in which operation was performed on the sinuses with resultant clearing of the chronic otorrhea.

In conclusion, the author states that (1) in the great majority of the cases the chronic purulent otitis media can be cleared up, the perforation of the drum can be closed, the function of hearing, and the health of the patient can be restored by surgical drainage of the purulent sinusitis; (2) in those cases in which the mastoid process has become involved the drainage of the purulent sinusitis will greatly facilitate the measures taken to clear up the involvement of the mastoid process; (3) as long as the activating purulent sinusitis is left undrained, local treatment will prove unavailing and time-consuming.

The manner in which chronic purulent otitis will clear up following surgical drainage in a suitable case is startling and dramatic.

JOHN F. DELPH, M.D.

Fenestration of the Labyrinth. O. Popper. *J. Lar. Otol.*, Lond., 1946, 61: 441.

The author reports in some detail the transtympanic approach for fenestration of the labyrinth. He states that his greatest problem in carrying out this approach was not the instrumentation, but the question of illumination, stereoscopy, and magnification.

The author states that the hazards in this work are very formidable, but under control as long as the surgeon can see. Therefore, he describes and discusses in some detail the headgear which he has designed to help supply the proper illumination and magnification of the operative field. Briefly, it is a headgear with a strong light and lenses which both magnify and light the operative field, as well as giving stereoscopy. A diagram of the headgear is pre sented.

The author discusses the anesthetic that he uses in carrying out his operation and he does not believe that the type of anesthesia is as important as the anesthetist. He is not greatly in favor of local anesthetics, but prefers general anesthetics—any of the various types, as long as they are given by a competent anesthetist.

Before the beginning of the operation, the patient's head is placed in proper position and the skin is prepared in the usual manner. His incision is marked out in a brilliant green—a line running vertically down for about an inch and a quarter immediately in front of the tragus from the incisura tragi to a point somewhat in front of the lobule. He then infiltrates the temporomandibular cleft with a solution of saline containing 6 to 8 minims of adrenalin (1 in 10,000) to the ounce. He uses a fine needle and the point is directed backward, so as to hug the lamina tragi during the whole injection. The incision is made along the marking, now somewhat distorted by the infection. From now onward the operation may be conveniently described as falling into eight stages, as follows:

1. Exposure of the tragal cartilage and the cartilage of the external auditory meatus. The anterior surface of the tragal cartilage is freed and, once this is achieved, it provides a point for insertion of the

closed blades of a medium sized Killian speculum. The blades are gently opened, and the whole tragal cartilage is cleared in very short time. The whole of the latter is exposed down to its attachment to the edge of the tympanic plate. An incision along its edge is made and the periosteum carefully reflected. Then the closed Killian blades are placed between the periosteum and the denuded tympanic plate and gently separated. The tympanic plate should be exposed for just over a quarter of an inch.

2. Separation of the cartilage from the edge of the tympanic plate. The author finds that this is very easily done with the use of the Killian blades. Small slivers of broadish cartilage may remain on the edge and they are removed in Stage 3.

3. Removal of portion of the tympanic plate. A long-bladed retractor is used, and the posterior blade engages the free edge of the cartilaginous meatus and flattens the latter out against the bony posterior wall. The anterior blade pushes forward the temporomandibular joint plus anterior tissues that are present. When this is done, the drum is clearly seen with its vital landmarks. The edge of the tympanic plate is nibbled down with a rongeur until the entire drum is exposed to view. The author uses a Reiter's automatic mallet for this procedure.

4. Fashioning of the tympanomeatal flap and exposure of attic wall and middle-ear contents. An incision about half an inch from the drum down to bone is made, sweeping around the remaining portion of the bony meatus. The skin is gently reflected from the meatus and, by working all the way around, the skin is folded over the drum, its periosteal surface facing the operator. The meatal skin and drum become continuous at the tympanic ring. The posterior segment of the latter is detached from the sulcus tympanicus so that the meatal skin plus the posterior half of the drum may be folded over the handle of the malleus. After this, the superlative landmarks in the middle ear are revealed. The meatal skin plus the attached drum are gently tucked into the recess between the remaining portion of the tympanic plate and the anterior part of the drum. The greatest care must now be taken not to tear the tympanomeatal flap with the use of the burrs. The author believes that only diamond burrs should be used as they require less pressure and are far less damaging to soft tissues, should the latter be accidentally touched.

5. Removal of attic wall and exposure of incus. The operator uses a cylindrical diamond burr of 1½ mm. diameter. The object is to drill a hole right through the attic wall to reveal the continuation of the incus in the attic space. Through the drilled hole the incus can be seen and the edges of the hole are then enlarged until the attic wall has been taken down in all directions. The body of the incus, its short process attached in the antral region, and its articulation with the head of the malleus anteriorly are now exposed. This is practically all the bone removal that has to be done and the author believes that this minimal destruction of bone is responsible for his not having any cases of otorrhea postoperatively.

6. Removal of the incus and exposure of the dome of the vestibule and facial canal. The main attachments of the incus are severed and the incudomalleolar articulation is now broken and the incus very carefully removed, care being taken not to injure the chorda tympani. When this is done, the dome of the vestibule, the facial canal, and other important landmarks can be seen.

The author also mentions an alternative technique to expose the dome of the vestibule, but he does so with hesitation, and the discussion is not in detail. He hesitates to mention it because the surgeon is deprived of most of his valuable landmarks with his alternate technique. This technique involves stages 4, 5, and 6.

7. Enchondralization of the dome of the vestibule. The author uses a flat-ended or spherical-headed diamond burr for this procedure and the entire dome is ground down flat to a level below the facial canal. Bone dust and debris are removed by suction irrigation every few seconds, using a solution of 100,000 units of penicillin in 20 c.c. of saline. The facial canal and all other structures are under direct vision of the operator and they should not be injured if sufficient care is taken. The author does not use the mobile cartilaginous stopple of Lempert as he believes that it is the size of the fistula more than anything else that keeps the fistula open.

8. Replacement of the tympanomeatal flap to cover the fistula. The field is carefully cleansed, and when this is done it is found that the drum falls back into its accustomed place without tension or torsion. The meatal portion of the tympanic flap is placed over the dome of the vestibule, its periosteal surface closely adapted to the fenestration. Narrow ribbon gauze impregnated with vaseline and sulfanilamide is gently packed on top of it and into the meatal passage. The other end of the strip is pulled through the intact meatus from below.

The postoperative care is mentioned, and the author states that his results have been good and that he has had very little vertigo and spontaneous nystagmus afterwards, and what occurs usually disappears after the third day. His patients usually begin to hear much better immediately after operation, even with the packing within the ear.

The author discusses a hypothesis to account for hearing improvement after fenestration in otosclerosis. He presents this hypothesis based on the premises that sound transmission occurs through the round window. He considers the tympanic membrane to have three main functions: (1) it is the most perfect receptor for sound; (2) it assists by variations of tension to "focus" for sound; (3) it protects the organ of Corti by (a) an immediate tympanostapedial reflex, and (b) by relaxation, curtaining, and dampening sound vibrations.

The author briefly mentions some of the treatments used previously for otosclerosis which were all without value. He believes that the fenestration

operation is the procedure of choice, that it will be found more successful as time goes on, and that his manner of the transtympanic approach, in particular, will gain acceptance and will be considered the best approach.

The article contains some very excellent colored plates of the different steps in the operation.

WILLIAM A. AHROON, M.D.

Tumors Involving the Petrous Pyramid of the Temporal Bone. Bruce Proctor and J. R. Lindsay. *Arch. Otolar.*, Chic., 1947, 46: 180.

The petrous portion of the temporal bone may be involved by tumors originating within the temporal bone, by tumors arising from adjacent structures, and by tumors metastasizing from distant primary foci.

The origin and the pathologic characteristics of meningioma involving the temporal bone are discussed. A case of meningioma of the temporal bone, complicated by acute labyrinthitis superimposed on chronic labyrinthitis produced by the tumor, is presented.

A case of sarcoma of the temporal bone is presented, and the pathologic characteristics of the tumor are pointed out. Occasionally a tumor of this type is confused with meningioma.

The salient features of diffuse sarcomatosis of the meninges are briefly discussed and illustrated. When sarcomatosis involves the eighth nerve it may be clinically confused with neurofibroma, acoustic neurinoma, or meningioma. In the case of diffuse sarcomatosis presented in this report, a small focus of otosclerosis was found in each labyrinthine capsule in addition to bilateral involvement of the eighth nerve.

Neoplasms originating in the pons, e.g., gliomas, may extend into the internal auditory meatus and interfere with the functions of the seventh and eighth cranial nerves.

A case of bilateral neurofibromatosis of the eighth cranial nerve in which psammoma bodies were observed in both of the internal auditory meatuses is presented. Since these psammoma bodies are usually found associated with meningiomas, their presence in conjunction with neurofibromatosis suggests a possible closer relationship between meningiomas and neurofibromatosis than has previously been suspected.

One case of metastatic tumor of the temporal bone is presented. The bone marrow of the petrosa is capable of filtering out tumor cells circulating in the blood stream and becoming a secondary focus for a new growth.

Tumors involving the petrous pyramid of the temporal bone are relatively uncommon, present a wide variety of types, and produce such a multiformity of subjective and objective symptoms that it was deemed advisable to report some of the more unusual cases observed at the University of Chicago Clinics where the temporal bones were obtained for histopathologic examination.

The following types of tumors have been among those reported as primary in the temporal bone: meningioma, sarcoma, squamous cell carcinoma, plasma cell myeloma, hemangioma, epidermoid, dermoid, malignant melanoma, cylinder cell epithelioma, and adenocarcinoma. JOHN F. DELPH, M.D.

NOSE AND SINUSES

Malignant Melanoma of the Nasal Mucosa. Charles C. Grace. *Arch. Otolar.*, Chic., 1947, 46: 195.

Through the years, the question of the source of malignant melanoma of the nasal mucosa has been a matter of controversy. Wilkinson, presenting the earliest report in the British literature, in 1912, remarked that it was then generally accepted that these tumors arise in certain cells, stellate or spindle in form, occurring in the skin and the choroid, and less frequently in the mucous membranes of the nose and the mouth.

In the opinion of Ewing, the melanoma is a pigmented tumor arising from a specific mesoblastic cell, the chromatophore, or from tactile cells lying in the epidermis, or from nerve cells in the dermis.

In the upper portion of the nasal cavity the epithelium of the olfactory mucosa is filled with an abundant supply of granular pigment. It would seem reasonable that this upper nasal mucosa with its wealth of pigment should offer a site as favorable for the development of a melanoma as the richly pigmented surfaces of other parts of the body. However, this is not the case, for these tumors arise in the mucosa that is without pigment, either in the septum or in the lateral wall, including the turbinate.

In 63 of the cases mentioned in the literature, the initial site was given as the nasal cavity in 17 patients, the septum in 21, the inferior turbinate in 14, the middle turbinate in 4, the middle and inferior turbinates in 1 patient, the lateral wall in 4 patients, the floor of the nose in 1 patient, and the external ala in 1. In the case presented by the author, the melanoma arose in the inferior turbinate.

Usually the first symptom is unilateral nasal blockage, which is soon associated with recurrent epistaxis. Occasionally, the hemorrhage is frequent and profuse. Pain is not often a symptom unless the tumor has grown to the extent that there is pressure, or unless there is blockage of a sinus. The discharge of a blackish or inky-black serous fluid is frequently present.

Although pigmentation is usually present in great degree, it is not an invariable criterion in the diagnosis of this lesion. The histologic picture without the assistance of melanin may have to be the guide. The dopa reaction is of value in these instances for it indicates those cells which are true melanoblasts containing the oxidase ferment capable of transforming the colorless chromogenic material in the blood into melanin.

As to treatment, radiotherapy seems to be generally unavailing. Irradiation in addition to surgical intervention was employed in the treatment of 18

patients (43 per cent of the 42 cases in which therapeutic measures were described in any detail), without appreciable benefit.

The slow growth of the primary tumor as compared with the rapid dissemination of the metastatic lesions is an important consideration in treatment. Simple removal of the tumor, although apparently complete and followed by irradiation with radium or roentgen rays, seems to be of no permanent benefit. Radical removal, including a wide margin of normal tissue, would appear, however, to offer a reasonable chance of cure. Often in a nasal operation, such removal cannot be performed without resulting deformity and impairment of function, but it should nevertheless be undertaken even though the lesion is small.

A case of malignant melanoma of the nasal mucosa occurring in a negro 81 years of age is reported in detail. JOHN F. DELPH, M.D.

PHARYNX

Tracheotomy in Bulbar Poliomyelitis. Robert E. Priest, Lawrence R. Boies, and Neill F. Goltz. *Ann. Otol. Rhinol.*, 1947, 56: 250.

During 1946, 1,830 patients with poliomyelitis were treated in Minneapolis. Approximately 400 were diagnosed as "bulbar" cases. Tracheotomies were performed in 75 of these. Twenty-nine of the tracheotomy patients survived. Of this group, 17 lived because of tracheotomy, 2 probably lived because of tracheotomy, and 10 recovered after tracheotomy was done prophylactically.

Indications for tracheotomy included (1) respiratory distress as evidenced by recurrent cyanosis, coarse râles in the chest, and laryngeal stridor, (2) unmanageability causing the patient to resist pharyngeal aspiration, (3) stupor of sufficient degree to make the patient oblivious of secretion in his airway, (4) inability to cough effectively, (5) pharyngeal pooling of mucus, (6) vocal cord paralysis, and (7) intralaryngeal hypesthesia as demonstrated by laryngoscopy.

Cyanosis can be diagnosed clinically only when anoxia is far advanced and irreversible damage has already occurred to already diseased neural tissue. Tracheotomy should be performed before anoxia has produced damage of the nervous system. Aspiration bronchitis and pneumonitis, anoxia, and fatigue are minimized by keeping the airway clear. In 15 cases gross amounts of pharyngeal secretion or food, or both, were aspirated from the trachea at the time of surgery. Immediate relief from anoxia resulted, with general improvement in the condition of the patient. No deaths were attributed to tracheotomy. Intermittent pharyngeal aspiration by nasal catheter was found to be superior to continuous suction. All patients have been decanulated but 1 adult who became physiologically dependent on her tube and 1 child who had a residual laryngeal paralysis. Tracheotomy in conjunction with artificial respiration will enable some critically ill poliomyelitis patients to survive until natural recovery of damaged neural tissue can occur. Seventeen case histories are presented. JOHN R. LINDSAY, M.D.

NECK

Intratracheal Goiter. Lars, Thorén: *Acta chir. scand.*, 1947, 95: 495.

The author reports a case of intratracheal goiter resulting in fatality because of stenotic symptoms. The patient was a woman, age 30, who had a prominent goiter dating from about the time of puberty. For a period of about 5 years she had experienced respiratory difficulties, which were aggravated premenstrually and in connection with two pregnancies. A probable diagnosis of intratracheal goiter was made on the basis of the history, clinical study, laryngoscopy, and roentgenograms. Because of the pronounced stenosis preparation was made for operation, but the patient died from suffocation, although intubation and other aids were performed. The suffocation may possibly have been due, to some great extent, to a reactive swelling and hyperemia after treatment with vascular constricting agents used in laryngoscopy. At autopsy and on microscopic examination, direct connections were found between the intratracheal goiter and the retrotracheal portion of the outer goiter via the cricotracheal membrane. The increase in size of the intratracheal portion in connection with the pregnancy and an adjacent acute laryngitis were probably decisive in the unfortunate outcome. There were no symptoms of thyrotoxicosis.

There are several theories regarding the genesis of intratracheal goiter. In some cases it most probably occurs on the basis of a total or partial detachment of parts of the thyroid glandular primordium (von Brun, Hulten). In other cases the source might be explained in accordance with the ingrowth theory (Paltauf, Wegelin) which is supported by Wegelin's investigations. The present case can be elucidated both by the ingrowth theory and that of Hulten.

Cases of slight intratracheal goiter may run their course without any appreciable symptoms. When symptoms occur the picture of the disease is dominated by stenosis in the upper air passages, which is usually slowly progressive. The first appearance of symptoms often occurs at puberty and exacerbations are prone to occur premenstrually and in connection with pregnancy. At laryngoscopy particular attention should be paid to the region below the vocal cords where the intratracheal goiter takes the form of a rounded, even curvature inwards in the subglottic space. The roentgen picture may be typical in some cases and of value in differentiating the lesion from an extratracheal goiter. If stenotic symptoms persist or recur after thyroidectomy for extratracheal goiter in patients in whom these symptoms have been prominent, one should suspect intratracheal goiter.

The treatment of the condition is operative. A simultaneous pregnancy constitutes no contraindi-

cation to operation but increases the indication. The intratracheal goiter is extirpated pertracheally or by laryngofissure. Recurrence is seldom encountered. The mortality of operation becomes high when extirpation is performed late and under unfavorable circumstances. JOHN L. LINDQUIST, M.D.

Thyrotoxic Crisis. Janet W. McArthur, Rulon W. Rawson, J. H. Means, and Oliver Cope. *J. Am. M. Ass.*, 1947, 134: 868.

This report is on 25 surgical crises and 11 medical crises which occurred among a total of 2,033 cases of thyrotoxicosis during 25 years. Twenty-five of these surgical crises followed 1,383 operations and 11 medical crises followed some precipitating cause. Sixteen of the surgical and 8 of the medical cases terminated fatally. The season of the year exerted but little influence on the frequency of the thyroid crises. The average age of the patients experiencing surgical crises was 46 years. The average age of those experiencing medical crises was 39.4 years. Ten of the 11 medical crises and 17 of the surgical crises occurred in women. Thus, a 1 to 3 ratio of males to females experiencing crises occurred. Eight of the medical and 12 of the surgical crises occurred in patients with diffuse goiter. Three of the medical and 13 of the surgical crises occurred in patients with toxic nodular goiter. The relative toxicity of the 2 types of goiter and the mortality rates almost coincided. The majority of crises occurred in patients with thyrotoxicosis of short duration.

A table is presented which summarizes the amount of weight lost between the time of onset and the time of admission to the hospital. Eleven tables are presented in detail which show summary of the data, the age incidence of thyroid crises, the duration of symptoms of thyrotoxicosis, the amount of weight loss, the basal metabolic rate on admission, the therapy prior to hospital admission, the incidence of complicating disease, the pathologic findings in autopsies of 12 patients who died of thyroid crises, the influence of age and complicating diseases on survival, the precipitating factors in the development of thyroid crises, and the factors influencing survival from surgical thyroid crisis.

Severe complicating diseases, especially heart disease, were common in thyrotoxic patients in whom a crisis developed, and exerted a significant influence on the survival of such patients. Postmortem findings showed that few patients had any demonstrable hepatic lesions but disclosed the frequent occurrence of cardiac and pulmonary pathologic conditions.

The precipitating factors which appeared to be provocative of crises were thyroidectomy (14 cases), pneumonia (7 cases), iodine withdrawal (4 cases), postoperative hemorrhage and secondary suture (3 cases), wound sepsis (2 cases), and digitalis intoxication (1 case). Patients who failed to gain weight and whose symptoms were not improved preoperatively did not survive thyroid crises.

Three case histories are discussed in detail and it is suggested that in every case of thyroid crisis therapy should be individualized to correct all the abnormalities. It is necessary to continue the administration of antithyroid drugs until the patient is in a suitable condition for surgery.

RICHARD J. BENNETT, JR., M.D.

Carcinoma of the Thyroid. Robert C. Horn, Jr., Robert F. Welty, Frank P. Brooks, Jonathan E. Rhoads, and Eugene P. Pendergrass. *Ann. Surg.*, 1947, 126: 140.

Although most thyroid cancer occurs in nodular goiters, the incidence of malignant tumors in nodular goiters has been regarded by many physicians as too low to be accepted as a valid indication for their routine removal. However, as the operative risk has declined, it has become probable that life can be saved by taking a more radical attitude toward nodular goiters. The use of postoperative radiotherapy has been a moot point, and it is with a view to clarifying this subject that the authors have reviewed all of the cases observed at the Hospital of the University of Pennsylvania, Philadelphia, for an 11.5 year period.

Seventy-one patients with carcinoma of the thyroid and 3 patients with lateral thyroid carcinoma were treated during this period. Sixty-two cancers of the thyroid were encountered among a series of 2,079 surgically treated patients with thyroid lesions, an incidence of 3.0 per cent. Among 1,135 surgically treated *nodular* goiters the incidence of carcinoma was 5.5 per cent.

Thyroid carcinomas occurring in the younger age groups tend to be the less malignant of the pathologic types of the condition and are less advanced in their growth when they first come under observation. Seventy per cent of the carcinomas in the authors' series occurred in patients between the ages of 40 and 70 years, and 76 per cent of the growths occurred in women.

The majority of thyroid carcinomas are of the papillary or malignant adenoma types, and these may be grouped together as grade I tumors, i.e., tumors of low grade malignancy. Fifty-eight per cent of patients treated for tumors of this type survived for a period of more than 5 years, and 60 per cent of the patients treated longer than 10 years ago are alive and well. Although the prognosis in tumors of other pathological types is poor, the 10 year survivals in the authors' series include 1 patient with a small cell carcinoma and 1 patient with a giant cell sarcoma.

The extent of the disease at the time treatment is instituted is more important prognostically than its pathological type. Eighty-six per cent of the patients whose tumors were discovered only on pathological examination and who were treated more than 5 years ago, are alive and well. Seventy-five per cent of such patients treated more than 10 years ago are alive and well.

Many patients with thyroid cancer develop metastases or recurrences 5 years or more after their initial treatment. This series includes 1 patient who

died with metastastis more than 10 years after thyroidectomy.

In view of the relatively small risk of operation, it would appear wise to recommend the surgical excision of all nodular goiters unless strong contraindications exist. The extension of carcinoma through the capsule of the gland indicates the institution of postoperative irradiation. It has been especially effective in the papillary carcinomas. The benefits of postoperative irradiation in cases in which the carcinoma has not extended through the capsule are not clear from the present study. So many of these patients do well that a considerably greater experience will be required before postoperative irradiation in this group of cases can be finally evaluated.

ERNEST D. BLOOMENTHAL, M.D.

Aberrant Papilliferous Cervical Tumors (Tumores papilíferos cervicales aberrantes. Parte anátomoclínica). **A. Bianchi.** *Arch. cubanos cancerol*, 1947, 6: 117.

Aberrant thyroid tissue may give rise to cervical tumors which can be found isolated in lymph glands or other associated lymphoid tissue. Because of the slow growth of these tumors and their malignant appearance, they are frequently mistaken for a malignant process, although a papilliferous structure may be found both in carcinomatous or noncarcinomatous tumors.

To overcome this difficulty of differentiation one must carefully study the histological appearance of the cells that cover the papillae, capsulation of the tumor, and, lastly, invasion of the blood vessels. Some papilliferous structures in the lymph glands may have their origin from malformed pharyngeal tissue, as, in the latter, epithelial and lymphoid tissues are side by side in the embryo. A fibrous capsule between the papilliferous process and the lymphoid or thyroid tissue is of diagnostic value as it indicates whether one is dealing with a malformation or a metastatic process.

ARTHUR F. CIPOLLA, M.D.

Nature and Characteristic Features of Laterocervical Branchiogenic Carcinoma (Natura e caratteristiche dei carcinomi branchiogeni laterocervicali). **Federico Pizzetti.** *Tumori, Milano*, 1947, 33: 25.

Some writers deny the existence of laterocervical branchiogenic carcinoma but the author advances valid arguments in favor of such a clinical entity. He bases his opinion on personal observations, and clinical, embryologic, and anatomopathologic data.

The generic term "branchiogenic tumor," "branchioma," or "cervical embryoma" is frequently applied to a variety of tumors.

The following conditions should be taken into consideration in the differential diagnosis: various types of carotid paragangliomas, lymphoepithelioma, rare epitheliomas deriving from an ectopic inclusion of salivary gland in cervical lymph glands, carcinoma of the thyroglossal duct, certain forms of pseudocarcinomatosis, mixed tumors of the salivary glands, and various types of connectivoma.

Two types of tumors originating from the branchial cleft may be distinguished: (1) benign, represented by branchial cysts and encapsulated adenolymphomas, and (2) malignant, represented by branchiogenic carcinoma in the strict sense of the word.

Among 100 cases of lateral tumors of the neck observed by the author, he found 11 in which the diagnosis of laterocervical branchiogenic carcinoma could be established. Only 2 patients were younger than 40 years. The tumors were located in the mesobranchial area and showed a relatively rapid growth. They were of hard consistency, and showed a tendency to adhere to the skin only in advanced stages. Secondary ulceration of the skin occurred in several instances. Metastases were found in the liver, bones, lungs, and regional lymph glands. The pharynx was secondarily invaded in 1 patient.

The autopsy revealed a typical macroscopic aspect of carcinoma with occasional necrotic or pseudocystic areas. The histologic examination established the presence of structures of ectodermic and entodermic origin.

JOSEPH K. NARAT, M.D.

SURGERY OF THE NERVOUS SYSTEM

BRAIN AND ITS COVERINGS; CRANIAL NERVES

Isolated Oculomotor Palsy Caused by Intracranial Aneurysm. Geoffrey Jefferson. *Proc. R. Soc. M.*, Lond., 1947, 40: 419.

In order to study each aspect or type of symptom found in cerebral aneurysms, the author discusses the occurrence of an isolated oculomotor paralysis as the essential feature. Fifty-five aneurysms out of a total of 158 had this isolated paralysis. Although it is agreed that the majority of patients had congenital aneurysms, it is believed that they probably developed later in life from congenital defects and, in a sense, may be compared to inguinal hernias appearing in later life.

The most common site is the distal portion of the internal carotid artery soon after entering the intracranial cavity by piercing the dura mater, and hence is supraclinoid in position. The posterior communicating artery may be either above or below the aneurysm. The constant features are that the aneurysm has a pear-shaped configuration and faces posteriorly. The aneurysm occurred on the basilar artery in only 3 of a total of 55 cases.

All portions of the oculomotor nerve are not equally involved. Although ptosis is the most common finding, many patients will note diplopia before the ptosis. The patients often stated that the eyelid felt heavy and that this, with the pain, caused them to close the eye, although after several days to a week they may awaken to find they are unable to open the eye. The pupil is at first classically dilated, but usually within 2 to 4 weeks may contract slightly. Recovery starts in several weeks regardless of whether the carotid is ligated or not. This is almost never complete, the least recovery occurring in the superior rectus muscle.

Pain is a very characteristic and distinguishing symptom. It is always in the ophthalmic division of the trigeminal nerve, ipsilateral forehead, and about the inner canthus of the affected eye. When associated with severe occipital headache and nuchal rigidity it is indicative of subarachnoid hemorrhage. Anesthesia is not usually present, but if it is, the aneurysm is subclinoid.

Subarachnoid hemorrhage occurred in 40 patients, or 70 per cent of the cases. Although it was fatal in 7 cases, while the patients were in the hospital, it is surprising to note that "nearly all immediate survivors are still alive."

Arteriosclerotic aneurysms were present in 10 per cent of the patients, about a third of whom were hypertensives. An important finding is that hypertension in the older age group is not an absolute contraindication to carotid ligation, since 2 patients, 57 and 56 years of age, had internal carotid and common carotid ligations, respectively, and were alive and apparently without ligation sequelae after 8 years in 1 case and after 6 months in the other. As might be expected, many of these patients are poor risks and do not warrant surgery, death usually resulting from angina or myocardial failure.

The differential diagnosis is seldom a particularly difficult problem. So-called ophthalmic migraine can be differentiated by a detailed and careful history revealing the absence of residuals. Carcinoma of the nasopharynx does not give an isolated third nerve palsy. Although the author encountered 3 pituitary adenomas with oculomotor paralysis, an associated visual field defect was found in all patients.

The surgical approach finally selected as the procedure of choice was ligation of the carotid trunk. In some cases the common carotid was ligated first and later the internal carotid; however, the results were as good in one as in the other. After a fatality from an attempt to clip the neck of an aneurysm intracranially, this procedure was discarded as too hazardous although intracranial carotid clipping, or ligation and trapping of the aneurysm is considered satisfactory. The former was performed in 23 cases. The operations on the 3 patients who died within a day or so were emergency ties, as the patients were semi comatose. One patient died 7 years later from an unknown cause; hence 19 patients have survived. In 3 other cases an attempted ligation was abandoned due to hemiplegic signs.

The most important criteria in suggesting surgery is pain, since it is felt that pain implies that some activity is occurring in or about the aneurysm.

The most astounding finding is that "few patients who remain pain-free come to any harm whether operated upon or not." JACK I. WOOLF, M.D.

Neurinomas of the Cerebellopontile Recess. A Clinical Study of 160 Cases Including Operative Mortality and End-Results. Antonio Gonzalez Revilla. *Bull. Johns Hopkins Hosp.*, 1947, 80: 254.

This study of neurinomas of the cerebellopontile recess was based on operations performed by Walter Dandy at The Johns Hopkins Hospital in the period from 1926 to 1945. There was a total of 160 cases, of which 145 were acoustic neurinomas, or those originating predominantly from the eighth nerve. There was an extreme variation in the ages of the various patients, ranging from 12 years of age to 69 years of age. The average age of the patients derived from the onset of symptoms was 39.6 years. The average age on admission to the hospital was 44.1 years; hence there was an average duration of symptoms before surgery of 4½ years.

Although the prominence of the elements varies in the symptomatology, the various elements were, nevertheless, present in most cases. Auditory and labyrinthine symptoms were present in every case.

They were noted as the initial symptom, however, in only 68.6 of the cases. Diminution of the auditory acuity was subjectively present in all cases despite the fact that there was no objective evidence of hearing loss in 5 cases. Tinnitus was present in 62.3 per cent of the cases. Cerebellar symptoms, such as unsteadiness in walking, staggering, clumsiness, were present in 86.2 per cent of the cases. Headaches were not as frequent as noted in earlier reports; however, they were present in a little over two-thirds of the cases and were noted as the initial symptom in 12.4 per cent of the cases. The headaches were usually localized in the occipital region, although at times they were quite variable, extending from the suboccipital to the frontal region. Symptoms referable to the trigeminal nerve were found in 56.5 per cent. Numbness was usually the predominant sign, although an occasional case suggestive of a typical tic douloureux was noted. Evidence of involvement of the facial nerve was present in only 15.8 per cent. The sparing of the facial nerve remained a surprising finding, as has been noted in the past.

Audiograms were performed in all cases, except 1. Some degree of impairment was noted in 95.8 per cent of the cases. This was found to be as follows: there was total deafness in 107 cases and partial in 32. Although 5 cases showed no abnormal changes in the audiogram it should be noted that these cases showed disturbances in vestibular function. The cold caloric test for vestibular function was not performed routinely. Among 87 cases, however, in which it was used there was a loss of caloric response in 66 cases and a partial disturbance in 11.

From these findings it was concluded that one would expect involvement in some portion of the eighth nerve in all cases of acoustic neurinoma. It is disclaimed, however, that all acoustic neurinomas arise from the vestibular portion of the nerve; rather, the author believes that they may arise from either the vestibular or the auditory branch, as has been proved by the work of Hardy and Crow.

The operative mortality rate has diminished with the evolution of newer approaches as advocated by Dandy, with the natural improvement in technique which occurs over the passage of years. With the unilateral cerebellar approach and careful intracapsular dissection there was a mortality rate of only 6.5 per cent in patients operated upon in the last 8 years. The author reports the astounding figure of only 2.4 per cent, or 1 fatality, in 41 patients who were operated upon in the past 5 years.

An analysis of the operative deaths reveals that neither age nor symptoms have any particular correlation with the cause of death since there was no greater predominance in either young or old patients nor any correlation with the severity of the symptoms. A surprising finding was a very definite increased mortality rate in males. The average weight of the tumors removed was 27.6 gm. The greatest primary cause of death was direct trauma to the brain stem. Other factors were meningitis, pulmonary complications, and vascular complications.

Although the importance of preserving the facial nerve is well recognized and emphasized, this could be done in only 9 cases. Needless to say, it was felt that despite the great desire to save the facial nerve, the possibility of adherent tumor capsule to the nerve made it necessary to sacrifice it in most cases. X-ray evidence of destruction of the porus acusticus was present in only 50 per cent of the cases. Hence, the absence of x-ray evidence of bone destruction of the acoustic canal should not hinder one in making the correct diagnosis.

The association of unilateral acoustic neurinomas with peripheral neurofibromatosis was found to be very infrequent since only 3 cases with this association were found in a series of 160 cases of cerebellopontile recess tumors. In studying this specific type of tumor it was noted that the age at the onset was definitely far below the age of patients with solitary neurinomas, that is, the age group revealed an average of 24.3 years. The average age at the onset of symptoms was only 14.3 years with a quite prolonged duration of symptoms (10 years). The symptomatology was very similar, however, to that of the type without acoustic neurinomas. At the time of operation, however, it was noted that the neurinomas were extremely hard, which made their removal by curettement a very difficult and extremely hazardous procedure. With the possibilities of other neurinomas and the possibility of development of meningiomas the final outcome was very bad. In the present series of only 3 cases there was 1 operative death, 1 death 7 years later from recurrence, and 1 patient living and well at the end of 6 years.

Bilateral acoustic neurinomas were found in 6 cases, representing 3.7 per cent. There was a rather definite relationship with von Recklinghausen's disease, since 3 cases, representing 50 per cent, showed definite evidence of peripheral neurofibromas. A more striking correlation was noted to be a hereditary transmission with familial predisposition. This was noted in half of the cases. The symptomatology was not a great deal different from that of other neurofibromas except that it was more similar to that of the cases of unilateral neurinoma associated with von Recklinghausen's disease; that is, this condition usually occurred in definitely younger individuals, the average age at onset being 17.8 years of age. The symptoms, however, were usually of somewhat shorter duration, probably because of the bilateral involvement. As would be expected, the operative mortality of such tumors is definitely higher because of the difficulty of operating on 2 sides and the greater possibility of edema resulting from operation in a reduced space. Hence, the best procedure in operation is a bilateral cerebellar approach with extirpation of the tumor in 2 stages.

Neurinomas of the fifth nerve are comparatively rare, comprising 3 cases of the present series. The symptomatology was very similar to that occurring in acoustic neurinomas with the exception that trigeminal symptoms preceded auditory and labyrinthine disturbances by an average of 4½ years. In 2

of the patients the symptomatology was that of tic douloureux. There was no immediate operative mortality. However, a careful follow up could not be obtained in any case. An interesting finding was that in 1 case there was a marked return of auditory function following operation.

Neurinomas of the tenth nerve occurred in only 2 cases. There was 1 very definite and predominant symptom found in both cases, and this was hoarseness which was the initial symptom in 1 of the cases. The remainder of the symptoms may at times represent quite a problem. However, as a whole they might mimic any cerebellopontile recess tumor or an acoustic neurinoma. There was no operative mortality in this group.

Only 1 case of neurinoma of the eleventh nerve was found, and in this case there was a very definite connection with the generalized neurofibromatosis.

JACK I. WOOLF, M.D.

Penicillin in the Prevention of Infection during Operations on the Brain and Spinal Cord. J. B. Pennybacker, Margaret Taylor, and Sir Hugh Cairns. *Lancet*, Lond., 1947, 2: 159.

A study was made of the local use of calcium penicillin powder mixed with sulfamezathine in the prevention of infection of operative wounds in brain and spinal cord conditions. There were 5,000 units of penicillin per gram in the mixture. The powder was lightly insufflated onto the various layers of the wound, including the surface of the brain and spinal cord. At 40 operations an average of 1.4 grams (7,000 units of penicillin) of powder was used. In a study of one series of 24 cases of tantalum cranioplasty and a second series of osteoplastic craniotomies, 1 to 3 grams of powder were used, and it was found that penicillin was usually present in the wound in adequate bacteriostatic concentrations for 18 hours. The first 24 hours are the most important in prevention of the establishment of infection.

No convulsive seizures followed the application of this powder to the brain. In some laminectomy wounds where a large surface of muscle was exposed, a slight excess of exudate was noted, and the wounds were drained through a small stab incision.

During the prepenicillin era from May, 1938 to November, 1944 there were 1,169 "clean" major cerebral and spinal operations performed at the authors' hospital. Among these, 51 cases were infected, and in 13 cases the infection was fatal. From December, 1944 to March, 1947 penicillin sulfamezathine powder was insufflated locally into 670 similar type wounds with the result that there were 6 wound infections with no fatalities from these complications. Thus the incidence of infection was cut from 4.4 per cent in the prepenicillin era to 0.9 per cent with local application of the penicillin-sulfamezathine powder.

The powder gives only slight assistance to the body in overcoming wound infection. It does not prevent virulent infections nor does it replace any of the measures used to combat infection at the operating table.

RICHARD C. SCHNEIDER, M.D.

SPINAL CORD AND ITS COVERINGS

Peripheral Extension of Radiopaque Media from the Subarachnoid Space. J. Douglas French and William H. Strain. *Surgery*, 1947, 22: 380.

In a series of 200 consecutive myelograms, 4 cases were encountered in which pantopaque extended outside the normal confines of the subarachnoid space, apparently along the nerve roots. A report of these 4 cases is presented. In one case a definite anatomic abnormality was demonstrated at operation. The second case was one of subarachnoid block just above the point of injection, and extension of the medium along the nerve root was thought to be due to anatomic changes which developed as a result of a chronically obstructed arachnoid space, as well as pressure alterations produced by the injection of additional fluid into a small closed space, and also probable injection directly into a nerve root rather than into the subarachnoid space. In the third case, the probabilities are that the material was injected outside the subarachnoid space. In the fourth patient, injection is thought to have been made presumably into the perineural spaces of the nerve root.

The author has conducted experimental work on rabbits and dogs, with injection of radiopaque media in the peripheral nerves and into the subarachnoid spaces of the spinal canal, under normal and increased pressure conditions; in another group, injections were made into the intracranial subarachnoid space under physiologic pressures.

Under normal pressures, it was found that the opaque materials made rather rapid exit from the intracranial spaces, through the cribriform plate, into the nasal secretions and cervical lymphatic system. Extension of radiopaque material from the lumbar region was never observed under physiologic conditions, but did occur into the perineural spaces when excessive pressures were applied, or the animal was killed.

Peripheral injections of nerves indicated that there may be a connective tissue plane organized from the dural perineural sheaths which form discrete channels in such a fashion as to subdivide the progressively branching nerve into longitudinal compartments supporting axis cylinder extension.

No evidence could be found to indicate that there is a physical communication normally between the spinal subarachnoid space and the peripheral nerves. Under unusual circumstances, such extension may occur along the nerve sheath from the subarachnoid space.

HOWARD A. BROWN, M.D.

PERIPHERAL NERVES

Injuries of Peripheral Nerves in Two World Wars. W. Rowley Bristow. *Brit. J. Surg.*, 1947, 34: 333.

The author discusses the influence of Sir Robert Jones on surgery of the peripheral nerves, and gives a brief résumé of his work in this field.

A further discussion ensues with reference to developments in peripheral nerve surgery during World

War I, including end-to-end suture, assessment of results from nerve graft (which was uniformly poor) and the conclusion that neurological recovery always fell short of perfection, under the best operative conditions.

The use of splints to overcome and prevent deformity is described, although it is also stressed that preserving joint mobility is essential. Physiotherapy was apparently used more in World War I than in World War II, in the British Army.

The operative technique employed in World War II is outlined, and includes wide anatomical exposure, alterations in position of the limb, stripping of branches, transposition of nerves, bulb suture, the two-stage operation, and bone shortening. Suture of the sheath with stainless steel wire and fine nonabsorbable thread is recommended. Protection of the suture line with nonabsorbable material proved unsatisfactory.

The problem of primary and secondary suture is discussed, and ideas for and against these procedures are presented. It would appear to be evident that delayed suture (2 or 3 weeks after injury) may have some advantages; in some series, a greater percentage of success in delayed sutures is reported, in contrast to primary sutures.

The author is inclined to believe that delayed suture is not advisable unless there is good reason to delay, as in an open wound with potential infection.

Bone shortening may allow an end-to-end suture which otherwise would be impossible.

Neurolysis is not considered a very valuable procedure, although the author has not clearly defined what he considers a neurolysis to be.

Composite tables have been set up to assess motor and sensory recovery. These include various degrees of sensory recovery and motor improvement; a review of the tables permits a ready evaluation of a case, or group of cases. Recovery in various nerves has been considered, and the radial nerve again heads the list of recoveries. Recovery in median nerve injuries follows. In injuries of the upper extremities, recovery in the ulnar nerve was poorest.

In the lower extremities, medial popliteal sutures showed a fairly good degree of recovery, while lateral popliteal results were poor.

Nerve grafting, both heterogenous and homogenous, was considered a failure.

HOWARD A. BROWN, M.D.

Surgical Experiences with Peripheral Nerve Injuries. Herbert J. Seddon. *Q. Bull. Northwest. Univ. M. School*, 1947, 21: 201.

About 2,500 cases of peripheral nerve wounds in military and civilian personnel were studied in England and Scotland at 5 centers devoted exclusively to treatment of this type of injury. The classification of types of peripheral nerve injury devised by Professor Henry Cohen was used, namely, neuropraxia, neurotmesis, and axonotmesis.

In neuropraxia there is no axonal degeneration and no change in the muscles supplied by the affected nerve. The essential lesion is presumed to be due to fragmentation of the myelin sheath. Recovery is complete and rapid.

Neurotmesis is defined as an injury in which fibers of one kind may grow into tubes leading to end organs of another kind; as a result the axon is wasted with subsequent imperfect innervation.

In axonotmesis the fibers may grow into a Schwann tube of the proper kind but leading to a destination different from the one originally served by that particular fiber. As a result there is a permanent impairment of 2 point discrimination sensibility, weakness in individual muscles, and imperfect participation in synergic movements.

In regeneration there is a progressive diminution in the rate of growth, the process becoming slower as it approaches completion. Nevertheless, the rate may be approximately constant over moderately long periods, and in man is roughly from 1 to 1.15 millimeters per day. The decrease in rate of regeneration may be due to progressive shrinkage of the Schwann tubes in the peripheral stump after section of a nerve. As a result the growth in diameter and myelinization are hindered, and both of these are essential to maturation and function. It was likewise noted that there were noxious changes in the muscle itself and that progressive atrophy had a retarding effect on reinnervation and function. Atrophy of a denervated muscle is reversible up to a certain point. Its greatest effect is that of interstitial fibrosis invading Schwann tubes where they approach their innervation. The proximal fiber is prevented from reaching its old motor end plate.

In general, primary nerve suture gives less satisfactory results than early secondary repair for the following reasons:

1. The extent of intraneural damage in a severed nerve cannot be adequately evaluated immediately, and it is only after a few weeks of growth that fibrosis of the damaged zones becomes apparent.

2. Suture of the epineurium is always carried out rather than suture of the nerve itself. This structure is usually quite thin at the time of injury. After a short interval a certain degree of thickening occurs which permits a firmer suture of the epineurium, and one that is more accurate in apposition.

Mobilization of the nerve stumps is essential to avoid tension at the suture line. In order to accomplish this it is necessary to expose larger areas of tissue with the risk of spread of infection.

A review of 1,681 cases during this period showed that 41.5 per cent required surgical repair. A breakdown of these figures is given. In considering nerve grafting it was believed that heterogenous grafts were a failure, homogenous grafts were moderately good, and autogenous grafts were most successful. The factors involved in nerve grafting are discussed. In a series of 58 cases of autogenous grafts the degree of regeneration was sufficient to justify the procedure in more than 50 per cent of the cases. In general, the results were encouraging when the severity of these wounds is considered, and the author no longer

regards autogenous nerve grafting to be merely an experimental procedure.

RICHARD C. SCHNEIDER, M.D.

An Operation for Nerve Pedicle Grafting. F. G. St. Clair Strange. *Brit. J. Surg.*, 1947, 34: 423.

The author reports a method of nerve grafting employed in one patient with injuries involving both the median and ulnar nerves in the forearm. No follow-up studies, to indicate the result, are reported.

The author recommends the method in an attempt to improve the circulation to the graft, but it would require a situation in which two nerves were involved, and one must be sacrificed in an attempt to improve the second.

In this case, the proximal ends of the two nerves were identified and resected until satisfactory nerve bundles were found. These two nerves were then approximated, both being proximal segments.

At a second stage operation, about 6 weeks later, the ulnar nerve was freed at a considerably higher level than the point of suture of the two proximal ends, and was then divided. The nerve was then swung downward and carried through a tunnel so that it could be approximated to the distal portion of the median nerve below.

The author believes that such a pedicle nerve autograft may have application in certain special situations of the type here described.

HOWARD A. BROWN, M.D.

Regeneration of Severed Nerves. Lewis J. Pollock, James G. Golseth, Frank Mayfield, Alex J. Arieff, and Others. *J. Am. M. Ass.*, 1947, 134: 330.

The authors present evidence that regeneration of a distal segment of an injured nerve occurs in spite of separation of the segments. Proof of regeneration is seen when there is recovery of voluntary motion, recovery of sensation in the isolated supply of a nerve, histologic evidence of fibers in the distal segment, response of muscles to direct electrical stimulation of the nerve, and reactions of muscles which show there is no complete denervation, when they are stimulated electrically. A chronaxia of less than 15 milliseconds for response to faradic stimulation and a galvanic tetanus ratio of more than 1.0 satisfy the latter requirement. The galvanic tetanus ratio of a completely denervated muscle is 1.0. Since regeneration and degeneration proceed simultaneously, there may be instances in which the galvanic tetanus ratio may never be found to be 1.0.

Eighty-four cases were selected for study. The ends of the nerves were separated by gaps up to 9 cm. in length. Only in 1 case did stimulation of the distal segment produce a response when it was studied at the time of the original operation.

At surgery very few instances of a galvanic tetanus ratio of 1.0 were found, some being as high as 29.0. When the cases were studied after suture, the ratio was less than at surgery, but still above 1.0 in most instances. On later examination, the ratio again rose. These changes in the galvanic tetanus ratio indicated that nerves degenerate and spontaneously regenerate. Histologic material was available in some instances and the presence of neurofibrils substantiated the belief that regeneration had occurred.

DANIEL RUGE, M.D.

SYMPATHETIC NERVES

The Surgical Treatment of Hypertension. The "Neurogenic" Versus Renal Hypertension From the Standpoint of Operability. Geza de Takats and Edson Fairbrother Fowler. *Surgery*, 1947, 21: 773.

The authors present case histories of 18 patients who had bilateral thoracolumbar sympathectomies for hypertension. In addition, they give a table which groups 50 patients into 3 categories: 8 with nonrenal hypertension, 23 with renal hypertension, and 19 unclassified.

To meet the requirements of a nonrenal hypertension, the following conditions must be present: (1) normal renal structure in a hypertension of long standing; (2) history of a previous thyroidectomy for a toxic goiter; (3) the finding of a medullary or cortical tumor of the adrenal gland.

It is generally assumed that nonrenal or neurogenic hypertension is the ideal type for splanchnic nerve section. Some workers have made an effort to differentiate neurogenic from renal hypertension by the response of the patient's blood pressure to high spinal anesthesia. The authors' experience, however, has not supported the view that the nonrenal hypertensives do better after operation than those with definable renal damage. The authors perform renal biopsis at the time of sympathectomy. The types of renal pathology demonstrated were unilateral hypoplastic kidney, renal trauma, post-toxemia, pyelonephritis, and streptococcus nephritis.

The conclusions reached are that the so-called neurogenic group has not responded well to sympathectomy, whereas the renal group, provided renal damage is not too advanced, has responded favorably. Patients who have had pyelonephritis, post-toxemic hypertension, streptococcus nephritis, and rheumatic renovascular damage are favorable candidates when the original process has subsided and the resulting renal arteriolar sclerosis remains. Probably the neurogenic type of hypertension is not mediated by the sympathetic nervous system.

DANIEL RUGE, M.D.

SURGERY OF THE THORAX

CHEST WALL AND BREAST

Nerve Blocking Therapy for Fractured Ribs. D. J. Richardson and E. M. Papper. *J. Thorac. Surg.*, 1947, 16: 432.

The application of regional nerve blocking to the therapy of disease or injury has often been made with the primary purpose of controlling the associated pain. Experience with 230 patients has shown that paravertebral injections of analgesic solutions are indicated to eliminate the pain of fractured ribs, and are definitely useful to prevent more serious complications and to reduce mortality.

A variety of solutions was used in the treatment. The most common solution was procaine, 1 to 2 per cent, which, in about two-thirds of the cases, was followed by the injection of 1 to 2 c.c. of absolute alcohol. Other solutions used were procaine and ammonium chloride, intracaine, monocaine, and several experimental drugs. The results varied but little.

Following the initial injection, there was almost immediate relief of pain in 80 per cent of the cases. Less than 25 per cent of the patients required more than one treatment. Among the patients presented, 93.5 per cent had multiple rib fractures, and more than a third of the entire series had major complications associated with trauma.

The mortality rate in the complicated cases was 12 per cent and the total mortality was 4.1 per cent. These results indicate that pain relief with nerve block is of significant value in preventing pulmonary infections and death of patients with fractured ribs.

SAMUEL KAHN, M.D.

Treatment of Cancer of the Breast with Estrogenic Hormones (I preparati estrogeni ed il cancro della mammella). **V. Pricolo.** *Tumori*, Milano, 1947, 33: 46.

The following conclusions are drawn by the author from observations on 18 patients with cancer of the breast who were treated with estrogenic hormones.

The administration of estrogenic hormones has a definite effect on the primary tumor and the metastases although the effect is only of a transient character. The hormones have a beneficial effect on the painful phenomena and the general condition of the patient. The results are especially noticeable in elderly women, particularly during the menopause. The administration of estrogens should not be considered a substitute for surgery, radiosurgery, or the administration of radium.

Estrogens are indicated in inoperable cases because the patient's life may be prolonged.

The author recommends the repeated administrations of moderate doses, such as from 100 to 200 mgm. per series of treatments. High doses should be avoided especially in adolescents and women during the period of sexual activity.

The author usually injects from 5 to 10 mgm. of estrogen daily or on alternate days until a total dose of 200 mgm. has been reached. In this manner, the toxic effects of estrogen, such as nausea, vomiting, grave hemorrhages from the breast or the tumor, metrorrhagia, thermic reactions, dermatitis, and edemas may be avoided.

JOSEPH K. NARAT, M.D.

The Use of Testosterone Propionate in the Treatment of Advanced Carcinoma of the Breast. The Treatment of Osseous Metastases. Julian B. Herrmann, Frank E. Adair, and Helen Q. Woodard. *Surgery*, 1947, 22: 101.

The subsequent course in 3 cases of osseous metastases reported previously (*Ann. Surg.*, 1946, 123: 1023) and the results obtained in an additional 11 patients with osseous metastases are presented.

The favorable results obtained in the present series were with smaller amounts of testosterone propionate than previously used. Dosages successfully employed were 100 and 200 mgm. biweekly and 100 mgm. triweekly. Less satisfactory results were obtained with biweekly doses of 50 mgm. Treatment is usually continued until the patient becomes asymptomatic.

Bone lesions appear to remain quiescent for a variable length of time after androgen therapy is terminated. When pain recurs it can be controlled by additional therapy.

Symptomatic improvement was evident within 2 weeks in 8 of the patients. In 6 patients roentgenologic evidence of calcification in metastatic areas appeared and in some this was discernible in 4 to 6 weeks after institution of therapy. Repeated irradiation of bones does not destroy their power to react to androgen. Effective dosage probably requires sufficient amount to render the patient amenorrheic. In many instances a favorable status may be maintained until pulmonary or liver metastases appear, when the patient rapidly regresses and dies within a short time despite the continued administration of androgen.

In one case (Case 8) androgen had first appeared to activate the lesions and later to inactivate them.

There appears to be no relationship with the menopausal status and the results of therapy. Four of the patients were still menstruating, 3 were menopausal, and the menstrual status of 4 is not recorded. Ages varied between 39 and 62 years.

Undesirable sequelae are acne, facial hirsutism, and deepening of the voice. Increase in libido is noted in many patients.

FRANK B. QUEEN, M.D.

TRACHEA, LUNGS, AND PLEURA

Adenomas Arising from Small Bronchi not Visible Bronchoscopically. Herbert C. Maier and Walter W. Fischer. *J. Thorac. Surg.*, 1947, 16: 392.

Bronchial adenomas usually occur in the larger bronchi, and can be visualized through the broncho-

scope. The diagnosis is often established by microscopic examination of biopsy material removed endoscopically.

Five cases are reported, in which the tumor was located in a branch bronchus not accessible to the bronchoscope. In each instance, the tumor was large enough to be visible on x-ray. Since the tumor did not arise from a large bronchus in any of the cases reported, none of the patients had any history or symptoms of secondary pulmonary suppuration. Three of the patients were asymptomatic, one had several hemoptyses, and one had slight pain in the chest.

In 4 of the cases the tumor was located near the hilar area. These were treated by lobectomy. In the fifth case, the tumor was at the periphery of the lung close to the diaphragm; in this case a partial lobectomy was done. All the patients are now well.

Grossly, bronchial adenomas are moderately soft, being much softer than the typical carcinoma. Occasionally, lobulation is present. The tumor is usually reddish-brown in color. If a portion of the tumor projects into the mediastinum, small veins often cross its surface.

In most instances, a portion of the tumor can be enucleated from the adjacent pulmonary tissue or mediastinal tissues, but there is no cleavage plane in the region of the bronchus of origin. If the tumor projects into an interlobar fissure, it may be noted that when the pleura is divided over the tumor, that portion of the tumor which projects towards the adjacent lobe can be readily freed, so that lobectomy is feasible. Pneumonectomy is not necessary in cases of bronchial adenoma that are typical and so located that the tumor can be completely removed by lobectomy. In none of the 5 cases reported was there involvement of the regional lymph nodes.

SAMUEL KAHN, M.D.

An Unusual Hamartoma (So-Called Chondroma of the Lung). Morris A. Simon and Harry C. Ballon. *J. Thorac. Surg.*, 1947, 16: 379.

Although small so-called chondromas in the lung are encountered occasionally as incidental findings at autopsy or on routine x-rays, the occurrence of relatively large, intrapulmonary cartilaginous masses which produce clinical symptoms is quite uncommon. Usually, so-called chondromas vary from a few millimeters to 3 to 4 cm. in diameter, but a few tumors varying from 5 to 15 cm. in diameter have been seen. They may be subpleural in position, or may lie near the hila or elsewhere in the lung. They are firm, dense, tend to be somewhat lobulated, are sharply demarcated, and are gray and glistening on section. The smaller tumors rarely, if ever, produce clinical symptoms.

These so-called chondromas are not pure cartilaginous tumors, but contain abnormal mixtures of the elements normally encountered in the bronchial wall. They are, therefore, more properly referred to as hamartomas or hamartoma chondromatosum pulmonis.

Although hamartoma of the lung is usually considered to be a benign, slow growing tumor, malignant changes may occur. In the case reported, the tumor was of unusual size, produced constant pain and mucopurulent expectoration, and presented a roentgenologic appearance which strongly simulated the usual bronchogenic carcinoma.

SAMUEL KAHN, M.D.

Cupola Tumors. Sven-Gösta Sjöberg. *Acta. med. scand.*, 1947, 128: 138.

Over 80 cases of cupola tumors have been described in the literature up to 1942. This type of tumor was first described by Pancoast in 1932. Horner's syndrome, first described by Hare in 1838, was based on a case of superior sulcus tumor (cupola tumor).

The author reports 5 cases of this type of tumor—(1) a squamous cell carcinoma, (2) a pleural endothelioma, (3) bronchial carcinoma, (4) bronchial carcinoma; in the fifth case a biopsy was not made. Four of the 5 cases exhibited Horner's syndrome.

One case, that of a bronchial adenocarcinoma, developed entirely above the pleural cupola and, except for a narrow adhesion, was entirely unconnected with the lung. It was also remarkable because of the lack of roentgenographic changes characteristic of "cupola" tumors. The author prefers this designation because "they are always intimately connected with the cupola pleurae."

Roentgen therapy had a good palliative effect in 3 cases. Unrelenting brachialgia and Horner's syndrome are the most important symptoms.

FRANK B. QUEEN, M.D.

Bronchogenic Carcinoma; a Clinicopathological Study of 36 Autopsied Cases Seen at the Brooklyn Cancer Institute between 1937 and 1945, Inclusive. William A. Henkin. *Ann. Int. Med.*, 1947, 27: 243.

Bronchogenic carcinoma constituted 9 per cent of all malignancies studied at autopsy at the Brooklyn Cancer Institute, Brooklyn, New York. Eighty-eight per cent of the carcinomas were seen in males of a mean age of 55.1 years.

All primary bronchogenic carcinomas arise from an undifferentiated stem cell located in the basal layer of the bronchial epithelium. The tumor is an adenocarcinoma, a squamous-cell carcinoma, or an undifferentiated or anaplastic carcinoma, depending on the type and degree of differentiation of the original stem cell. Tumors falling into the different histological categories have similar clinical courses, metastasize in a similar manner, and show no consistent variations in their response to radiation therapy.

Because different series, classified by equally competent pathologists, show tremendous variations in the percentages of the various histological types, classifications may be regarded as of academic rather than of practical significance.

The earliest and most common symptom, frequently overlooked for months, is a nonproductive

cough. The growing tumor is a foreign body which the bronchus attempts to extrude.

Physical examination and chest roentgenograms show no evidence of the disease in this stage although bronchoscopic biopsy is often possible at this time. In middle-aged individuals, wheezing or asthmatic breathing should initiate a thorough search for bronchogenic carcinoma, as the growing tumor begins to cause partial obstruction of the bronchus and the segment of lung distal to the affected bronchus becomes emphysematous. Usually the period of emphysema is of short duration and remains unrecognized while the enlarging tumor gradually produces complete bronchial obstruction and atelectasis. If the occluded bronchus is sufficiently large there may be a considerable shift of the mediastinum to the affected side, and a real decrease in functioning lung volume and dyspnea will develop. Almost simultaneously secondary infection develops within the atelectatic segment as necrotic tumor tissue, mucus, pus, and bacteria accumulate. Leukocytosis, fever, and anemia appear. This cycle is responsible for the dangerous diagnosis of "recurrent pneumonia" which has been made too frequently in the face of an advancing malignancy.

Roentgenologic diagnosis is not always easy; a definite diagnosis of bronchogenic carcinoma is made in about 60 per cent of the cases.

In the last analysis bronchogenic carcinoma can be established only by the microscopic examination of an adequate biopsy specimen. In early cases the specimen is obtained either at bronchoscopy or at thoracotomy. In later stages subcutaneous nodules or involved lymph nodes can be biopsied. Pleural fluid may contain cells whose appearance is suggestive of malignancy. Sputum is rarely examined and almost never shows malignant cells when studied by older techniques However, aspiration of bronchial secretions at bronchoscopy and staining by Papanicolaou's method is a procedure which should be performed more often.

The mean and the median life expectancy in this series were only 8 months from the onset of symptoms to death. No patient lived longer than 28 months after the appearance of symptoms.

Treatment is either surgical or roentgenological, or both.

If trained thoracic surgeons are available and there is no discoverable evidence of metastasis, the earliest possible surgical intervention is imperative. Interval roentgen study of a suspicious pulmonary mass or hilar enlargement dooms the case that is suitable for resection.

Every case without metastases or evidence of local invasion of vital structures should have the benefit of an exploratory thoracotomy. Roentgen therapy, although merely palliative with the generally available 200 kilovolt apparatus, should be given as early as possible after the determination of nonresectability. Tumor doses above 5,000 roentgens should be administered if maximum benefit is to be derived.

STEPHEN A. ZIEMAN, M.D.

Primary Carcinoma of the Lung, with Invasion of the Ribs. Frank Philip Coleman. *Ann. Surg.*, 1947, 126: 156.

Osseous invasion is present in probably between 5 and 10 per cent of all patients with carcinoma of the lung. The majority of the pulmonary carcinomas which secondarily invade adjacent ribs or vertebrae are of the squamous cell type. The author describes the case histories of 6 patients in whom such squamous cell tumors were observed. Pericostal invasion of the soft tissue of the chest wall without osseous extension had occurred in an additional patient in whom the tumor was an adenocarcinoma.

Peripheral pulmonary squamous cell carcinoma invades contiguous structures, grows slowly, and metastasizes late in the course of the disease. Because of this favorable pathologic behavior, it is emphasized that adjacent rib invasion does not relegate carcinomas of this type into the group of incurable tumors. Block excision of the chest wall, leaving a margin of healthy tissue attached to the involved structures, plus total pneumonectomy and excision of the regional lymph nodes is the desired treatment in such cases.

Other than pain, there are few symptoms until late in the course of the disease. Tenderness over the affected rib is usually present. Rib destruction is revealed by over-exposing the roentgen films. Direct biopsy of the rib will establish a tissue diagnosis but it carries with it the danger of soft tissue implantation in apparently operable patients.

Exploratory thoracotomy is the method of choice in selected cases for determining tissue diagnosis and operability. The pleural cavity is entered a rib and a full rib's interspace below the lesion. Involvement of the brachial plexus, sympathetic trunk, phrenic nerve, or the transverse processes of the vertebrae contraindicate curative surgical attempts but palliative resection may be considered in view of the associated severe pain.

Five of the 7 patients whose cases are reported by the author were subjected to block excision of the chest wall and pulmonary resection. A total pneumonectomy was carried out in 4 patients, and a palliative lobectomy in 1 patient. There was one operative death, and the patient with the palliative lobectomy lived for a period of 11 months. The 3 remaining patients are living and well—one, 6 years, one, 2 years, and one, 5 months after operation.

ORVILLE F. GRIMES, M.D.

Sequelae of Pneumotomy (Séquelles de pneumotomie). **Marc Iselin.** *Helvet. chir. acta*, 1947, 14: 147.

Recent advances in chemotherapy have rendered pneumotomy almost superfluous as a treatment for lung abscess. However, some cases fail to respond to penicillin, and pneumotomy may save the patient's life if not too long delayed. The mortality rate of this operation is estimated at about 25 per cent, but it is due to the sequelae of operation rather than to the intervention per se. Poor results of the operation are notably diminished if it is performed in

the earlier stages, before the development of chronic disease. Among the lesions responsible for noncicatrization following pneumotomy may be mentioned bronchial fistulas, residual pulmonary cavities, bronchial dilatations, and pyosclerosis.

The surgical pathologic anatomy of these complications is discussed at length, including that of the skin wound and surrounding bone structures. Frequently multiple cavities are present before the pneumotomy and may require repeated pneumotomy via the same or other routes for final obliteration. In the case of symptomatic fistula, treatment must be directed to the cause, whether this be multiple abcesses, bronchial dilatations, or abscesses superimposed on bronchial dilatation or pyosclerosis. For residual fistula, muscle flaps from the vicinity may be used to fill the cavity. In untreated symptomatic fistula, death usually ensues within 2 years from chronic suppuration, pneumonic phases, secondary hemorrhage, or cerebral abscess. In residual fistula the chief danger is from secondary hemorrhage which may cause sudden death. Even though the fistula is apparently well tolerated, its elimination is imperative. Differential diagnosis includes elimination of tuberculosis and cancer. In symptomatic fistula, tomography and bronchography will reveal the condition of the lung and bronchi. Roentgenoscopy at frequent intervals is a valuable diagnostic aid. In residual fistula a lipiodol bronchogram is necessary to ascertain the condition of the bronchial tree.

The surgical methods of treatment in order of increasing importance are as follows: débridement of the wound, repeated pneumotomy, plastic muscle flap operation, and lobectomy or pneumonectomy.

Symptomatic lesions must be treated in as rapid sequence as possible, only enough time being left between the operations for the reaction from the last to subside. Collaboration of the physician and surgeon in this respect is most important.

The choice of procedure will depend upon the lesions found. In the presence of a retracted wound with retention and hemorrhages, débridement under local anesthesia is indicated with incision of the scar tissue and liberation of the fibrous bands binding the skin to the deeper tissues. During operation poorly exposed cavities may be discovered and may require incision or even additional rib resection. Following wide exposure, the wound may be powdered with septolix and packed with gauze. Débridement was done 17 times in 12 patients, and 3 times in 1 patient. Repeated failure of this procedure is one of the major indications for the plastic muscle operation.

A secondary abscess close to the pneumotomy wound may be approached through the same incision following débridement. If the abscess is at a distance from the original wound a new approach may be required. In 1 case as many as 4 incisions had to be made. In the attempt to open an abscess once it is located great care should be employed to keep trauma to the lung tissue at the minimum. "Cuneoresection" with the thermocautery or electric bistoury too often involves trauma which leads to a fatal issue.

Should parenchymatous and bronchial suppuration persist, exeresis or typical lobectomy is indicated if the general condition of the patient permits. Because of the pulmonary breach, an aseptic intervention is impossible, and the operation is rendered still more difficult by the presence of regenerated bone and adhesions. Medical treatment is therefore recommended in these cases, and at least 1 patient who was believed lost was saved by this method.

In cases of fistula or residual cavity, a pedicled muscle flap from the vicinity may be used to fill the bronchial orifices, but this procedure is merely palliative and cure will not be complete if bronchial dilatation persists. Only 1 death was attributed to this type of treatment. The radical procedure for these lesions consists in lobectomy, which at present, with the aid of penicillin, permits complete cure in 3 weeks. Because of parietal changes this operation is difficult and dangerous. Adhesions are usually dense, the pneumotomy wound may be placed inconveniently, and, if more than 2 rib segments are wanting, the incision may be difficult to close. Diffuse induration may be discovered beyond the planned field of operation which necessitates a pneumonectomy. In such cases a prompt decision is imperative if the life of the patient is to be saved. Too much blood and time may be lost in performing a futile lobectomy.

If the general condition is good, the operation may be selected according to the anatomic findings; if not, no major operation can be attempted until proper measures have been instituted to strengthen the patient.

The pedicled muscle flap is indicated in tuberculous lesions in which exeresis might lead to dissemination of the bacilli. The residual fistula ordinarily left after this procedure will close in time. When the cavity is larger than a small fist, muscle transplantation will not suffice. In 1 case, healing took place after repeated plastic interventions over a year, and in another similarly treated case the bronchial fistula persisted but its caliber was greatly diminished. Complete success was obtained in 2 cases in which lobectomy was done in the first place.

Lobectomy of the upper lobe is extremely difficult and dangerous, whereas the plastic operation employing a pedicled muscle flap yields good results. In lower lobe and lateral lesions, exeresis is preferable.

For a successful plastic operation, the fistula must be permeable both on inspiration and expiration. Otherwise emphysema and purulent effusion may develop following operation in spite of the use of penicillin.

Other conditions permitting, exeresis is indicated when bronchial dilatations are found in the vicinity of the residual cavity or at a distance from it. In their absence and barring other contraindications, the plastic operation is preferable. These indications will, of course, be influenced by the constant advances being made in the technique of exeresis with diminished chances of hemorrhage and shock. The strongest argument against exeresis is the impossibility of

locating lesions before operation, so that pneumonectomy may be required where lobectomy was planned. Advances in chemotherapy permit an earlier evaluation of the probable results of medical treatment, so that when failure appears imminent, a pneumotomy can be done at a stage when the mortality and morbidity of this operation are still low and good results can be expected. EDITH SCHANCHE MOORE.

The Use of Prosthesis to Prevent Overdistention of the Remaining Lung following Pneumonectomy. Julian Johnson, Charles K. Kirby, C. S. Lazatin, and J. A. Cocke. *Surgery*, 1947, 22: 179.

The clinical experience and experimental work of these authors indicate that it would be desirable to prevent mediastinal shift following pneumonectomy and thus avoid overdistention of the remaining lung. This can be accomplished by an extensive thoracoplasty. In the presence of infection the thoracoplasty must be done. In the absence of infection it is desirable to use some method which is less extensive than a thoracoplasty whereby overdistention of the remaining lung can be prevented.

It is suggested that a noncompressible prosthesis may be introduced into the pleural cavity at the time of pneumonectomy as a means of preventing postoperative mediastinal shift and overdistention of the remaining lung.

Two types of prostheses have been studied in the dog: (a) a solitary large hollow metal prosthesis of zirconium, and (b) multiple small hollow plastic balls of methyl methacrylate (lucite).

The studies made indicate that hollow balls of methyl methacrylate (lucite) make a satisfactory filling material to place in the pleural cavity following pneumonectomy. They cause minimal reaction in the pleura and offer a convenient means of filling pleural cavities of various sizes.

STEPHEN A. ZIEMAN, M.D.

HEART AND PERICARDIUM

Anomaly of Aorta Simulating Mediastinal Tumor. David B. Corcoran and Frank Philip Coleman. *J. Thorac. Surg.*, 1947, 16: 427.

Roentgenologic examination is the most important method of diagnosis of solitary tumors of the mediastinum. It offers valuable information pertaining to the type of the tumor by localizing the mass, revealing its relationship to adjacent structures, and by establishing the presence or absence of pulsation. Diagnostic roentgen therapy also plays a role in the differential diagnosis in certain cases, by determining radiosensitivity.

A case of unusual interest is reported, in which a unique anomaly of the aorta, simulating a mediastinal tumor, was found. SAMUEL KAHN, M.D.

Complete Division for the Patent Ductus Arteriosus. Robert E. Gross. *J. Thorac. Surg.*, 1947, 16: 314.

A follow-up study of 43 patients who were treated by various types of ligation "in continuity" for patent ductus arteriosus shows that 80 per cent of the patients obtained complete closure of the ductus. In about 10 per cent of the cases the fistula was reestablished when the ligatures apparently cut partially through the ductus. In the remaining 10 per cent, the ligatures were not tied tightly enough, so that a small shunt persisted at the close of the operation. Most of the patients were benefited because the work of the heart was tremendously decreased, and in some cases a streptococcus viridans infection was permanently cured. However, permanent closure of the shunt can only be assured by complete division of the ductus.

Fig. 1 (Johnson *et al*). A dog sacrificed 2 months after left pneumonectomy and introduction of 24 one inch lucite balls into the pleural cavity. The right lung was not overdistended. There was just enough fluid present to fill the space between the balls (35.0 c.c.). There was minimal reaction of the pleura.

An anterior approach is made, and the third interspace is utilized after the second and third costal cartilages have been divided. The superior mediastinum is incised longitudinally one-half inch posterior to the phrenic nerve. The vagus and left recurrent laryngeal nerves are spared from injury. Lymph nodes, fat, and areolar tissue must be cleared away from the aortic arch and the pulmonary artery so that the intervening ductus can be clearly visualized. After the ductus has been freed of areolar tissue and has been cleared of any investing membrane, four clamps are applied and the ductus is divided between the middle two. The clamps used are standard Crile clamps, 5½ inches in length, the jaws of which

have been ground off on both sides so that the surfaces are nearly parallel and the jaws thinner than those of stock instruments.

The pulmonic side of the ductus is closed first. The presenting clamp (the one nearest the operator) is removed, thus providing a small cuff of ductus wall 2 or 3 mm. in length. This cuff is sewn over and over with a continuous 5–0 Deknatel silk suture carried on a small atraumatic needle. The aortic cuff produced by removing the uppermost clamp is treated in a similar manner. A second row of adventitial sutures is unnecessary.

After the pulmonic and aortic ends have been sutured, a gauze sponge is inserted into the interval between the pulmonary artery and the aorta and the remaining pulmonary clamp is removed. The pack is held in place several minutes to allow blood to coagulate between the interstices of the sutured end of the ductus. The aortic clamp is removed similarly. Only in a few cases is it necessary to apply additional sutures. The mediastinum is closed by repairing its parietal pleura with interrupted silk sutures.

Complete division of the ductus arteriosus has been carried out in 90 patients ranging in age from 2 to 46 years. There were 2 surgical deaths—one 2 weeks after operation, from an overwhelming staphylococcal mediastinitis, the other in a 26 year old female with advanced cardiac decompensation.

Complete division is especially indicated in adults beyond 18 to 20 years of age. The ductus is frequently unyielding, is difficult to compress, and has an exaggerated pulsation transmitted to it by a sclerotic and fixed aorta. Under such circumstances ligation in any form will occasionally lead to a partial recurrence of the fistula. Even in infants, the author believes that complete division is the superior method although it is admitted that in children in whom the ductus is soft, yielding, elastic, and easily compressible, ligation can almost always be relied upon to produce a permanent closure. Complete division of the patent ductus has been so completely satisfactory that the author has abandoned all forms of ligation of the vessel. ORVILLE F. GRIMES, M.D.

Complications of the Surgery of Patent Ductus Arteriosus. John C. Jones. *J. Thorac. Surg.*, 1947, 16: 305.

Complications of the surgery of patent ductus arteriosus in a series of 61 successive patients are reviewed. In 53 of the cases the ductus was ligated in continuity; in the remaining 8, it was divided and sutured. Virtually all patients developed postoperative effusions, but in only one-third of the cases was aspiration deemed necessary. Atelectasis occurred in 5 patients, each time in the left lower lobe. Left recurrent nerve paralysis occurred in 3 patients; it was persistent in 2 patients, and in 1 patient recovery was noted within a few weeks after operation. Two of the patients developed empyema thoracis, preceded by pneumonia in only 1 patient.

There were no wound infections. The anterior approach, utilizing the second interspace, has been abandoned because of the high incidence of keloid scars. A posterolateral incision with resection of the fourth or fifth rib is recommended.

Sudden copious hemoptysis was a serious complication in 2 patients whose case histories are recorded. Both patients, aged 35 and 11, had repeated episodes of gross hemoptysis. One patient remains well after exhibiting hemoptysis of varying degree for a period of 7 months, and occasional streaking of the sputum for a further period of 15 months. Exploratory thoracotomy performed on the 11-year-old patient revealed an aortobronchial fistula resulting from erosion by the silk umbilical tapes used in ligating the ductus. In both patients the ductus has remained closed. Since this experience the mediastinal pleura has been closed in all cases so that the knots are buried to protect the mediastinal aspect of the upper lobe. The latter procedure, however, will not prevent erosion of the aorta or possible aneurysm. Such a complication is considered an argument in favor of complete division of the ductus arteriosus.

There were 2 deaths in the series—one from Staphylococcus aureus endocarditis 48 days following ligation. In the first case, autopsy revealed a reestablished fistula between the pulmonary artery and the aorta, and an aneurysm of the ductus. The ligatures had cut through the wall of the ductus, and a superimposed blood stream infection resulted in vegetations on both the pulmonary artery and the aortic wall. The other death was an operative mortality from cardiac arrest occasioned by a considerable loss of blood at a rapid rate. At autopsy, cardiac pathology consistent with that found in rheumatic fever was revealed.

Failure to tie the tapes tightly enough to occlude the lumen of the ductus completely is the probable explanation of the failure to obliterate the continuous murmur which occurred in 5 cases. In 5 other cases, a recurrence of the continuous murmur detected from 5 to 6 weeks after surgery is explained by reestablishment of the fistula after the tapes had partially cut through the walls of the ductus.

ORVILLE F. GRIMES, M.D.

Bullet Wounds of the Heart (Heridas de bala del corazon). **Leonidas Aguirre Mac-Kay.** *Arch. Soc. hosp.*, Santiago, 1947, 15: 193.

This article records the experience of the emergency service for the City of Santiago de Chile between 1933 and 1945 (13 years). Fourteen patients with bullet wounds of the heart were treated, with 3 survivals. One of the 14 patients was not operated upon.

The subject of heart wounds is briefly reviewed with ample use of tables to illustrate the types of wounds, other associated wounds, the age, sex, state of sobriety, and the length of time elapsed between the wounding and the operation. These tables are taken not only from the material under discussion, but from records of the Medicolegal Institute and from the literature. No significant details of tech-

nique are included beyond illustrations of several accepted surgical approaches.

A case is reported in which a heart wound produced by a bullet was successfully sutured.

HIRAM T. LANGSTON, M.D.

Heart Catheterization. A. L. Johnson, D. G. Wollin, and J. B. Ross. *Canad. M. Ass. J.*, 1947, 56: 249.

The importance of more exact diagnoses of congenital heart lesions has been emphasized by the advances which have been made in surgery for congenital heart defects. Heart catheterization has been used by the authors in 17 children ranging from 19 months to 16 years. By this method all four heart chambers and the pulmonary artery and vein have been entered.

Forssmann, in 1929, is credited with the first heart catheterization, but it was not until the work of Cournand and Ranges, in 1941, that its many possibilities were recognized. Brannan, Dexter, and Baldwin also have reported recent works on this subject.

A ureteral catheter is introduced through a nick in the antecubital or saphenous vein. It is a special catheter with a curve in the distal end. This gives the operator some control in directing the tip. Under fluoroscopic control the catheter is passed into the right auricle, the right ventricle, and pulmonary artery.

Either arm may be used, but the catheter seems to pass more readily past the origin of the innominate vein on the left. A slow drip of saline through the catheter keeps the lumen patent. Blood samples or pressure readings are taken through a three way stop cock. The patient should be heparinized at the start of the procedure and a clotting time of 10 to 20 minutes is maintained for 24 hours afterwards. From 5,000 to 10,000 units of penicillin are given intramuscularly every 3 hours for 48 hours. Mean pressure readings are taken with a saline manometer and Tycos dial. Blood samples for oxygen determinations are withdrawn under oil and run by the Van Slyke method. An x-ray picture is taken at every site at which a blood sample is withdrawn. At the conclusion of the procedure blood is withdrawn from the femoral artery for an oxygen consumption determination, with use of the Benedict-Roth apparatus.

Morphine and scopolamine and a barbituate were used for preoperative medication. Intravenous morphine and avertin or pentothal were used as anesthetics in children under 3 years of age. The older children needed no anesthesia.

This method is safe, as some 1,200 procedures have been carried out without a fatality. No arrhythmias other than occasional extra systoles have been reported. The authors had one patient who developed paroxysmal tachycardia during the procedure. Only occasional slight thrombophlebitis of the brachial veins has been reported. One of the authors' patients, a 19 month old sickly infant, died 1 month after heart catheterization. A clinically unsuspected organized thrombus of the inferior vena cava, right renal vein, and both common iliac veins were present, as well as a large thrombus attached to the right auricular wall.

Of the 17 patients, 4 were cyanotic; 9 were considered to have interventricular septal defects; none were cyanotic; in 1 patient the persistence of a left superior vena cava was demonstrated.

Arterialized blood in the right ventricle or blood with a significantly higher oxygen content than that found in the right auricle is evidence of a ventricular septal defect. The case reports and x-rays of several examples are given.

An example of a patent ductus arteriosus and 2 cases of auricular septal defects are discussed.

In some instances, placing the catheter under fluoroscopic vision enables one to estimate the size of the ventricles or auricles.

Based on their limited experience and on the few cases in the literature, the authors believe that heart catheterization appears to be a useful adjunct to the investigation of congenital heart disease.

ROBERT R. BIGELOW, M.D.

Traumatic Pneumopericardium (Le pneumopericarde traumatique). **Éric Nègre.** *J. chir.*, Par., 1947, 63: 307.

Traumatic pneumopericardium produces its characteristic clinical syndrome of cardiac compression in addition to those symptoms which usually accompany all penetrating thoracic or thoracoabdominal wounds. In many instances the elements of the compression syndrome are not easily recognized in the complex picture of shock and acute anemia.

The pathophysiology of pneumopericardium is dependent upon the compressibility of gaseous substances and upon the exceptional faculty of the pericardium for resorption, which is superior to that of other serous cavities. However, intrapericardial gas may be under considerable tension, as in the case of hemopneumopericardium or of gas bacillus infection in which gas is continually produced in a nonextensible chamber. In the latter 2 instances the symptoms of cardiac compression rapidly ensue.

The compression syndrome of pneumopericardium is manifested by both respiratory and cardiovascular distress. Dyspnea is constant and respirations are rapid, short, and superficial. Anginal type of pain is common. Tachycardia, fall in arterial tension, increased venous pressure, deathly cyanosis or pallor of the face, and turgescence of the jugular veins completes the picture of compression. A precordial zone of tympany may sometimes be found but in most cases an intrapericardial or mediastinal outpouring of blood will mask such a sign. The roentgenological examination will confirm the existence of pneumopericardium alone or in association with a hemopericardium.

Pure pneumopericardium is rare and when present is produced by a rather small cutaneous wound with a short course directly to the pericardium. The more

usual finding is that of either a pleuropericardial or a pleuropericardioperitoneal wound resulting in injury to other viscera than the pericardium.

Uncomplicated penumopericardium does not carry a poor prognosis. That accidental insufflation of the pericardial cavity during therapeutic pneumothorax is innocuous is well known. However, traumatic pericardium is usually complicated by wounds of other viscera of the thorax or abdomen which considerably increase the severity of the complex.

Surgical exploration is imperative in all cases of traumatic pneumopericardium. In the pure case, intervention is first done to verify the integrity of the cardiac muscle, followed by repair of the pericardial wound. The simple excision of the cutaneous wound and its tract, and enlargement of the wound as necessary are recommended. In combined thoracoabdominal wounds resulting in pneumopericardium, attention should be given to the thoracic wound before the wounds in the abdominal cavity are treated. ORVILLE F. GRIMES, M.D.

ESOPHAGUS AND MEDIASTINUM

End-to-End Anastomosis of the Esophagus for Esophageal Atresia. Orvar Swenson. *Surgery*, 1947, 22: 324.

Primary anastomosis of the esophagus after closure of a tracheoesophageal fistula was performed on 14 infants. Multiple stage procedures, consisting of ligation and division of the fistula, gastrostomy, and marsupialization of the esophagus were necessary in 5 others. A gastroesophagostomy was successfully performed on a baby who had atresia without an associated tracheoesophageal fistula.

Changes in technique and in preoperative and postoperative care account for the improved mortality rate for primary anastomosis of the esophagus (6.6% in this series). Earlier diagnosis and the less common use of barium orally likewise have aided immeasurably.

The danger of aspiration of saliva is prevented by gentle suction on a soft rubber catheter introduced into the upper esophageal pouch. Oxygen, parenteral fluids, chemotherapy, and small transfusions of whole blood or plasma serve to prepare the infant for surgery.

A retropleural approach is made under cyclopropane anesthesia. Leaks in the anastomosis when the approach is made retropleurally are not necessarily fatal as a fistula develops which drains through the wound. Such fistulas usually close spontaneously without delay.

Once the mediastinum is entered by freeing the pleura from the thoracic cage and ligating and dividing the azygos vein, the fistula can be visualized. In order to secure maximum length to the lower esophageal segment, the fistula is divided close to the trachea. The tracheal opening is closed by a running fine silk suture as the fistula is being sectioned. Not more than 2 cm. of the lower segment should be freed because the blood supply is poor and ischemia is easily produced. The upper pouch is a sturdy structure due to hypertrophy and has an excellent blood supply, most of which originates high in the neck. It can therefore be freed extensively to gain considerable length. Traction sutures placed through the thickened wall of the upper pouch and the perivertebral fascia will relieve tension on the anastomotic line.

The esophageal ends are anastomosed by interrupted sutures in the muscular and mucosal coats anteriorly and posteriorly. The anastomosis must be water tight as the baby will swallow saliva soon after the conclusion of the operation. The catheter is removed from the upper pouch and a small rubber drain down to the anastomosis is left in place in the wound for 4 days.

Proper fluid, protein, and caloric intake must be supplied postoperatively to prevent generalized edema which is a common and serious complication. Edema is due chiefly to the low protein reserve of newborn infants, excessive fluids, particularly saline solution, low caloric and protein intake, and infection.

A Stamm gastrostomy is performed on the day following the primary anastomosis. Within 8 hours fluids are given by Murphy drip and in 18 hours a dilute formula is started. This is brought up to full nutritional requirements in from 48 to 72 hours, according to the condition of the patient. Oral alimentation is begun on the tenth day after surgery.

Some of the infants show fairly marked strictures on roentgen examination, but as long as the formula is taken well no dilatations are necessary. In 1 infant the lower esophageal segment was considerably scarred so that postoperative dilatations were necessary. ORVILLE F. GRIMES, M.D.

MISCELLANEOUS

The Influence of Positive Pressure Breathing on the Circulation in Man. Lars Werkö. *Acta med. scand.*, 1947, 128: Supp. 193.

In this monograph of some 120 pages, the author analyzes the effect on the circulation in humans of positive pressure breathing. Positive pressure breathing may be defined as respiration in which the pressure of the gases (air) at the mouth is artificially elevated. It may be of three types: continuous positive pressure breathing, expiratory positive pressure breathing, or intermittent positive pressure breathing, depending upon whether or not the pressure is artificially elevated during inspiration, expiration, or both.

The effects of these three types of respiratory pressure variations were observed in 14 patients having essentially normal circulation (no subjects free from known disease are, however, included) and 12 subjects with cardiovascular disease, predominantly arteriosclerotic or hypertensive in type.

The right heart was catheterized, the technique of Cournand being used to obtain samples of mixed venous blood and pressure tracings from the right heart.

Cardiac output was calculated according to the principle of Fick, directly, by sampling expired air, arterial blood, and mixed venous blood simultaneously. Pulse pressure was recorded from the right ventricle, the brachial artery, and (in 13 cases) from the pulmonary artery. In 3 cases the intrapleural pressures also were recorded.

Control values for cardiac output and blood pressures were obtained with the patient in a recumbent basal state. Pressure breathing was applied for 10 minutes and new values were obtained. In 20 or 30 minutes thereafter resting values were again obtained.

The specific effects on the circulation in humans of breathing air under varied pressure levels seemed to be variable, particularly in subjects with cardiovascular disease. By correlating the findings, however, particularly taking into account the cases in which data on intrapleural pressure changes were obtained, the following mechanism is suggested for the changes seen in cardiac output.

The pressures at each heart beat during the respiratory cycle showed that the net filling pressure (the end diastolic pressure minus the pleural pressure taken at the same moment) decreased during the phase of increasing mask pressure and increased during the phase of decreasing mask pressure.

It was believed that during the respiratory cycle in pressure breathing, the output of blood from the two ventricles is unequal. When the pressure in the thorax increases, the output from the right heart decreases as a result of reduction in right heart filling from the great veins, while the output from the left heart increases as a result of increased pulmonary venous return.

In patients with essentially normal circulation, the decrease in cardiac output during pressure breathing was closely correlated to the decrease in net filling pressure.

In patients with cardiovascular disease, in heart failure the increase in cardiac output corresponded to a decrease in net filling pressure in the right ventricle.

It is suggested that when intermittent pressure breathing is used for artificial respiration, the inspiratory period with high pressure should be short and the expiratory period should be long, with the expiratory mean mask pressure as near atmospheric pressure as possible, in order not to influence the circulation adversely.

In the treatment of pulmonary edema, intermittent, rather than expiratory, pressure breathing should be used as it puts less strain on the patient. The respiratory pressure can also be raised higher, if desired.

In the treatment of bronchial asthma and respiratory obstructive disease, the expiratory pressure should be kept at the lowest effective level, in order to have little adverse effect on the circulation.

This is a rather exhaustive appraisal of the topic, and the material is supplemented by many statistical compilations and data-filled charts.

HIRAM T. LANGSTON, M.D.

Ten Years of Thoracoplasty; A Statistical Study (Dix années de thoracoplastie; étude statistique). **George Deshaies, Girard Roland, and B. G. Bégin.** *Union méd. Canada,* 1947, 76: 665.

During the decade ending in February, 1943, 411 patients were subjected to thoracoplasty at the Sacré Coeur Hospital in Montreal. Of these, 196 were males and 215 females. The average age was 30.56 years, the youngest patient being 5 years, and the oldest 61 years of age. The surgical indications included pulmonary tuberculosis without empyema in 331 cases, or 80.5 per cent of the series, tuberculous empyema in 58 cases, or 14.1 per cent, and nontuberculous empyema in 22 cases, or 5.4 per cent.

The first group of patients, namely, those with pulmonary tuberculosis without empyema, was divided into 4 classes according to the severity of the lesions and prospects for recovery. The first class presented a small cavity in the right or left upper lobe close to the ribs in the axillary region. In these cases there was a moderate fibrous reaction, but no appreciable pleural reaction. The general condition was good and expectoration minimal, whether with or without bacilli. Gain in weight, absence of fever, and a favorable sedimentation rate indicated a recuperative tendency but there had to be no evidence of further lesions in the lungs or any other part of the body clinically or roentgenologically. Sixteen such cases were treated.

The second class included cases which presented a little larger lesion, a less favorable general condition, or a rather marked pleural reaction as seen in the roentgenogram.

The third class included the greatest number of patients, with extensive lesions involving more than one-half of the lung and occasionally with slight contralateral infiltration. The latter could be controlled by pneumothorax of the opposite side. The pleura of the same side may have been thickened by inadequate pneumothorax. In some patients the cavities were multiple and extended to the base of the lung and the general condition was only fair. This group included patients subjected to phrenicectomy.

Finally, in the fourth class were included the patients in whom thoracoplasty had been done merely as a last resort. Here the lesion was usually an enormous excavated lobitis, with some intestinal or osseous complication, serious contralateral involvement, and a poor general condition. Operation was usually refused in these cases.

Most of the patients had undergone cures of various types often over a prolonged period. Pneumothorax had been tried in 75 per cent of the cases. Of the 331 patients, 175 were subjected to costal resection on the right side, 159 on the left side, and 3, on both sides. The operation was done in two stages in 204 cases, 3 ribs being resected in each stage. A one-stage operation was done in 54 cases. In most cases in which a three or four stage operation was done, an anterolateral thoracoplasty was done in one stage. A new incision vertical to the anterior axillary line was used, and through the exposure the anterior costal

segments were resected up to the chrondrosternal cartilage of the ribs, three-fourths or four-fifths of which had previously been resected via the posterior paravertebral route. In a very few cases, these anterior segments were resected before the posterior segments. Usually the transverse apophyses of the second, third, fourth, fifth, and sixth ribs were resected. Apicolysis was added in some cases following the bony resection.

The mortality rate during the second five year period was greatly reduced, probably because of advances in bronchology, anesthesia, blood banks, as well as in radiologic and surgical technique.

Fifteen patients died following the first stage of the operation. Of 9 patients dying after the second stage, 1 had previously been operated on the contralateral side. Of 4 who died after the third stage, 1 had already been subjected to two stages on the other side. Twelve deaths were attributed to operative shock, and occurred early in the series before the day of blood banks and bronchoscopic drainage. Intratracheal anesthesia has also served to reduce the mortality. Other causes of death included bilateral parenchymatous reaction, homolateral reaction, controlateral reaction, secondary empyema, and infection of the wound, as well as accidental injury of the parietal pleura and empyema, fulminant hemorrhage from the wound, anesthetic shock before the fourth stage, secondary uremia, and incompatibility of the transfused blood.

Patients of the third or fourth class are more likely to have residual cavities even after several stages of thoracoplasty. However, a number of patients survived and some were even able to resume their occupation.

Of 303 patients surviving operation, 197, or 59.5 per cent, are living and of these, 131 patients, or 39.6 per cent, are working. Thirty four, or 10.3 per cent, are at home, either because they are afraid to go back to work or because they are still suffering from tuberculosis of one form or another. Thirty-two patients, or 9.6 per cent, are still hospitalized, and 77 patients have died from the results of operation or spread of the disease to the other lung or other organs. In many cases in which work was resumed too early, the disease spread to the other lung. Five patients died of causes not related to the operation or tuberculosis. Fifty-three patients, or 15.7 per cent, could not be traced.

The series of 58 cases of tuberculous empyema was divided into two classes, the good risks being those presenting a restricted pleural space with no detachment in the upper fourth, no evident bronchopleural fistula, and no marked pachypleuritis. Only 36 per cent of the series belonged in this class. It was noted that artificial pneumothorax had been employed in 35, 60.3 per cent, of the 58 cases in which tuberculous empyema developed. Thoracotomy for drainage was necessary in 30 cases, or 51.7 per cent. Extrapleural thoracoplasty sufficed in 33 cases. Thirty patients were subjected to a Schede thoracoplasty. Following resection of a portion of the parietal pleura, the infected pleural cavity was curetted. This intervention causes considerable surgical shock which may be difficult to control.

In 12 cases two types of thoracoplasty were done in the different stages. In some cases it was necessary to use a musculoaponeurotic graft to fill the pleural cavity.

The mortality of these patients without thoracoplasty was very high. Nevertheless, in 1945, 38 per cent of the patients were not only alive but working. The operative mortality rate was 15.5 per cent. Seventeen other patients have died subsequently, and 8 could not be traced.

It is evident that thoracoplasty is the only successful treatment for certain types of tuberculosis of the lungs and pleura. The risk is slight and many patients recover and can resume work.

EDITH SCHANCHE MOORE.

SURGERY OF THE ABDOMEN

ABDOMINAL WALL AND PERITONEUM

Femoral Hernia with Gangrenous Bowel. Clarence Dennis and Richard L. Varco. *Surgery*, 1947, 22: 312.

The published mortality rates for strangulated femoral hernia are high. Only one report in the literature mentions a mortality rate as low as 25 per cent. The authors believe that the high mortality statistics are due mainly to the conventional method of exposing and opening the hernia sac, either exteriorization or resection, and primary anastomosis in the contaminated field.

An alternative method of management is presented. Preoperative attention is directed toward re-establishing correct water and electrolyte balance. Gastric suction is instituted. Although the lapse of a few hours might increase the likelihood of frank gangrene in the strangulated bowel, it is wiser to attend to the altered fluid state.

With the use of local block anesthesia, a vertical incision is made over the bulge in the groin and cautiously carried down to the peritoneal sac. The contents of the sac can be visualized through the remaining wall. Should gangrenous bowel be recognized, dissection in this area is discontinued and an incision is made 2 centimeters above the inguinal ligament and parallel to it. The vertical line is continued upward to form a T-shaped incision. The incision is developed and the peritoneum is opened parallel with the oblique skin incision. From this vantage point, the viscera entering the hernia may be readily identified. If omentum is involved it is easily divided and ligated close to the neck. If gangrenous small bowel is present in the sac, Ochsner clamps are placed across the two limbs and the bowel is divided between each pair with the cautery. The inguinal ligament is then divided and split laterally, leaving enough aponeurotic tissue applied to the neck of the sac to prevent relaxation of the neck and release of the soiled content. The entire contaminated area can then be removed intact without soiling of the operative field (Fig. 1). Primary end-to-end anastomosis of the limbs of the bowel can then be accomplished.

Closure of the peritoneal defect in the repair of the hernia is easily accomplished because of the mobility of the peritoneum in this area. The margins of the internal oblique and the transversus muscles are sutured to Cooper's ligament as far lateral as the femoral vein and to the inguinal ligament lateral to that point. The inguinal ligament is restored by approximating it without tension to the lacunar ligament and to Cooper's ligament.

The importance of avoiding contamination is paramount. By recognizing the state of the contents through the intact hernial sac, contamination of the operative field is prevented. Experimentally it has been shown that the abdominal fluid and venous blood in cases of strangulating obstruction contain depressor substances. It is therefore important to resect the gangrenous segments of intestine without releasing the neck of the sac.

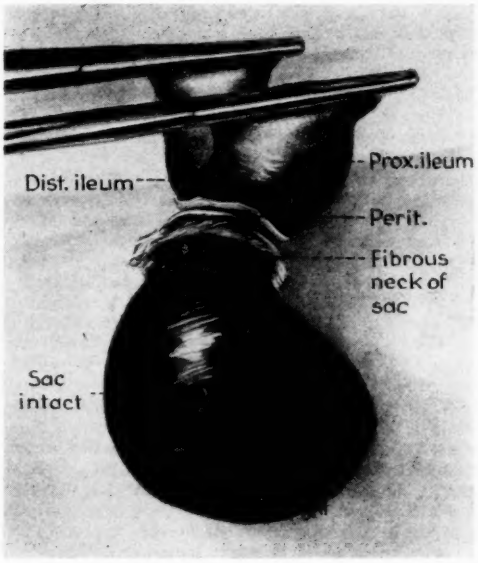

Fig. 1. (Dennis and Varco). Sac removed.

The authors defend their sectioning of the inguinal ligament by stating that the repair as indicated has been successful in their hands. Closed aseptic end-to-end anastomosis is recommended.

The authors present 10 cases in which this plan of management was carried out. Two patients have died, one of cardiac failure and the other of a ruptured aortic aneurysm. The other patients are living and well. One patient developed a recurrence as a direct hernia 2 years after repair.

ORVILLE F. GRIMES, M.D.

GASTROINTESTINAL TRACT

Effect of Enterogastrone on Mann-Williamson Ulcers in Dogs. H. C. Saltzstein, David J. Sandweiss, John M. Hammer, Edward J. Hill, and Henry J. Vandenberg, Jr. *Arch. Surg.*, 1947, 55: 125.

In this study the authors attempted to evaluate the effect of orally administered enterogastrone on a series of 15 dogs in which jejunal ulcer had been produced by the Mann-Williamson operation. At

the time of this report, the average survival time in the enterogastrone series was 96 days, while that of the control series was 71 days. The longest survival time in the enterogastrone series was 259 days, while that of the control series was 135 days. The shortest survival time in the enterogastrone series was 25 days compared with 13 days for the control group.

Eleven of the enterogastrone treated dogs died with jejunal ulcers with an average survival time of 97 days. Of the 11 dogs with jejunal ulcer, 10 had perforated ulcers and generalized peritonitis which accounted for death.

In the control series all of the dogs showed ulcer at autopsy, and in 72 per cent the ulcer had perforated.

Therefore, it is concluded that oral enterogastrone has some beneficial therapeutic effect on experimental Mann-Williamson ulcers in dogs.

HAROLD LAUFMAN, M.D.

Effect of Vagotomy on Mann-Williamson Ulcers in Dogs. H. C. Saltzstein, David J. Sandweiss, John M. Hammer, Edward J. Hill, and Henry J. Vandenberg, Jr. *Arch. Surg.*, 1947, 55: 130.

While 28 control dogs survived the Mann-Williamson operation for an average of 71 days, 12 dogs on which vagotomy plus the Mann-Williamson operation were performed survived only 51 days after the Mann-Williamson operation and 44 days after the vagotomy. Of the controls, 100 per cent showed ulcer at autopsy. Seventy-two per cent of these died of perforation with peritonitis. Among the vagotomized animals, jejunal ulcers developed in 6 of the 8 that lived more than 1 month after the Mann-Williamson operation. An inflammatory reaction of varying severity was found in the upper part of the jejunum in 7 of 12 dogs on which Mann-Williamson operations and vagotomy were performed. There was no correlation with the survival time. Gastric dilatation was present in 9 of the 12 dogs.

It is, therefore, concluded that vagotomy does not have a favorable effect on the ulcers produced by the Mann-Williamson operation. Since jejunitis was present in 60 per cent of the vagotomized dogs, it is suggested that it may be an explanation for the diarrhea following this operation.

HAROLD LAUFMAN, M.D.

Resection of the Vagus Nerves for Ulcer; An Interim Evaluation. Operative Technique and Hospital Management. Francis D. Moore. *Arch. Surg.*, 1947, 55: 164.

In this article the author outlines the technical procedures which he employs in vagus resection for ulcer, as well as the hospital management of patients. Eighty-seven per cent of the author's 84 patients had good results and are well satisfied with their operation from 2 to 30 months postoperatively. Five patients had a frankly poor result, either with a demonstrable recurrence or symptoms of ulcer. Five other patients had sufficiently severe side effects, consisting of diarrhea or other gastrointestinal manifestations, to detract materially from their satisfaction with the result. All but 1 of the author's patients were operated on through the thorax. Only 2 postoperative posterior gastroenterostomies have been necessary. Of 73 patients who underwent thoracic operations, 40 had no discomfort of the chest after the first few postoperative days, 31 had minor discomfort, and 2 had major chest or intercostal pain.

The postoperative management extends through the first 3 postoperative months and consists essentially of giving the stomach an easy mechanical job to perform and allowing it a complete 12 to 16 hour rest if the presence of fullness or diarrhea indicates some defect. Many patients who have been thus tided over a bout of motility symptoms have remained well subsequently. The author believes that although there is a strong temptation to carry out gastroenterostomy under these circumstances, it can usually be avoided.

The 19 patients in this series who had gastrojejunal stomas, either primary or secondary, had the same incidence of diarrhea and fullness as the series of patients with duodenal ulcer. This is another reason for not performing gastroenterostomy routinely. As treatment for frank obstruction, it is usually effective; as a means of avoiding gastrointestinal side effects, it is ineffective. The author describes his technique for the thoracic approach to the vagus nerves.

If care is taken in dietary management, the prolongation of hospitalization due to poor emptying of the stomach need only constitute a minor problem. The prevention of pulmonary complications involves early ambulation, the use of blow bottles, encouraging the patient to cough and to take deep breaths, and moving the patient freely in bed. To prevent postoperative dilatation of the stomach, the author gives less than 1 ounce of liquid per hour for 3 or 4 days. The diet is then cautiously increased with daily aspirations of the stomach. The diet is "set back" if a significant residue forms. The author leaves the Levine tube in place on suction for 48 hours in most cases. The patient is never discharged from the hospital following transthoracic vagotomy prior to the twelfth day.

By performing gastroenterostomy as rarely as possible, the author hopes to be able to better evaluate the therapeutic effect of the vagus resection. The routine performance of gastroenterostomy with each vagotomy confuses the therapeutic effect, since gastroenterostomy in itself has such an effect in most instances.

HAROLD LAUFMAN, M.D.

Section of the Vagus Nerves to the Stomach in the Treatment of Benign Gastric Ulcer. Paul V. Harper, Jr., and Lester R. Dragstedt. *Arch. Surg.*, 1947, 55: 141.

This article pertains to the treatment of patients with benign gastric ulcer by section of the vagus nerves. The rationale is based on the following considerations:

When the lesion is in the pyloric antrum and readily accessible, it is probably treated best by a sub-

total gastrectomy; however, when the lesion is high on the lesser curvature close to the esophagus, a resection extensive enough for the treatment of a possible malignancy would involve a total gastrectomy. Total gastrectomy is much more hazardous than partial gastrectomy, and the resulting digestive and nutritive defect constitutes a definite disadvantage. When these facts are taken into consideration, together with the small percentage of gastric cancers that can be cured by any type of surgical treatment, the authors believe a total gastrectomy is not justified in the absence of a definite diagnosis of malignant growth.

Of the authors' 250 cases of peptic ulcer treated by vagotomy, 8 were cases of gastric ulcer. Among these were 3 in which there was a coexistent active duodenal ulcer. In such cases the possibility of malignant growth is generally believed to be about 1 per cent. Therefore, when cases of combined gastric and duodenal ulcer are refractory to medical management, the authors believe that vagus section is indicated. In 3 such cases, healing took place extremely rapidly with no recurrence of symptoms. In 3 other patients in this series, large chronic gastric ulcers were present high on the lesser curvature of the stomach. These were refractory to medical and x-ray therapy. Subtotal gastrectomy as a method of treatment had been refused. In all 3 cases the ulcers healed promptly after vagus nerve section. All these patients remained well, 1 for more than 3 years, and 1 for more than 2 years.

The 2 remaining patients in this series also had chronic gastric ulcers high on the lesser curvature, but a differential diagnosis between benign gastric ulcer and carcinoma could not be made even with the aid of laboratory studies, roentgen examination, and gastroscopic observation. Palpation and inspection of the lesion at laparotomy were also not decisive. As a type of therapeutic test, vagus nerve resection was done. Although there was complete symptomatic relief in both cases, the ulcers failed to heal. Total gastrectomy was therefore advised.

The authors are of the opinion that unless the diagnosis of malignant growth is certain, gastric ulcers high in the stomach should be treated by vagotomy. If the lesion is benign, section of the vagus nerves may bring about prompt healing in ulcers that have proved resistant to intensive medical management. On the other hand, if healing does not occur within a period of from 4 to 6 weeks, the surgeon has additional evidence for the belief that the lesion is malignant and can undertake a total gastrectomy with a better conscience.

HAROLD LAUFMAN, M.D.

Clinical Evaluation of Complications Observed after Transthoracic Vagotomy. K. S. Grimson, G. J. Baylin, H. M. Taylor, F. H. Hesser, and R. W. Rundles. *Arch. Surg.*, 1947, 55: 175

Fifty-seven patients with refractory or frequently recurring peptic ulcer were treated by transthoracic vagotomy or transthoracic vagotomy plus gastroenterostomy. The persistence in using the transthoracic approach is explained by the assumption that it minimizes the chance of incomplete operation or of regeneration. The result obtained by questionnaire, office visits, and re-examination in the hospital indicated that 21 of 56 surviving patients are completely satisfied, 27 are almost completely satisfied, and 7 are only partially satisfied, while 1 was dissatisfied because of an exacerbation of a pre-existing gastrointestinal disturbance with vomiting and diarrhea. This patient died 2 years after vagotomy. There was 1 death 17 days after combined vagotomy and gastroenterostomy due to rupture of the stomach after an acute gastric dilatation and terminal massive hemorrhage from a jejunal ulcer. The greatest difficulty has been occurrence of obstruction at the outlet of the stomach with retention of the gastric contents and dilatation. Obstruction is usually due to abnormal function of the outlet of the stomach after removal of vagal control. Obstruction and retention have necessitated secondary gastroenterostomy in 5 patients from 11 to 105 days after transthoracic vagotomy. Two other patients with serious symptoms as the result of retention are being treated with partial success by parasympathicomimetic drugs.

Thirty-six patients were subjected to transthoracic vagotomy alone. Of these only 9 were completely satisfied with the results of the operation. Reasons for dissatisfaction consisted of vomiting during the first several months, hematemesis (3 cases), melena (1 case), recurrent severe pain (1 case), and colicky abdominal pain (2 cases). There were 28 instances of a sensation of fullness after eating, 18 instances of foul eructations during the first 3 months, with the persistence of these eructations in 10 patients. Of the 36 patients without gastroenterostomy, 20 who had been previously constipated had normal bowel habits after vagotomy, while 4 had moderate constipation. In 11 cases there was a continuous or periodical looseness of stools, and in 1 case a serious diarrhea.

Of 21 patients who had gastroenterostomy before, at the time of, or after, vagotomy, 6 had marginal ulcers occurring after subtotal gastric resection, 3 marginal ulcers after gastroenterostomy, 2 gastroenterostomy just before vagotomy, 5 gastroenterostomy at the time of vagotomy, and 5 gastroenterostomy after vagotomy. Of these 20 patients only 12 were completely satisfied, 5 almost completely satisfied, 2 partially satisfied, and 1 was dissatisfied. Unexplained serious episodes of colicky pain occurred in 3 patients. One of them had a stomal ulcer and a nonfunctioning gastroenterostomy 3 months after vagotomy. In 12 of these 20 patients there was a sensation of fullness after eating during the first 3 months after vagotomy, and this persisted in 6. The author found that vagotomy may be of value when combined with gastroenterostomy or when employed for stomal ulcer. He does not believe that transthoracic vagotomy alone should be used as standard treatment.

HAROLD LAUFMAN, M.D.

Partial Gastrectomy for Simple Ulcer. A. B. Watson. *Brit. J. Surg.*, 1947, 34: 353.

A follow up study of 132 patients who had undergone partial gastrectomy for simple ulcer was carried out in an effort to determine whether the results justified the operation. In the course of this study some undesirable side effects of the Polya operation were seen, which led to criticisms of this type of anastomosis. None of the patients had been operated upon less than 6 months previously. The results of the follow up are considered under the following headings: (1) clinical and functional result, especially in connection with the length of the loop and the width of the stoma; (2) the fractional test meal, with particular reference to the operation of pyloric exclusion; and (3) anemia.

The general impression gained from talking to these patients is that the operation of partial gastrectomy is definitely worth while, and this impression is confirmed by the statistics. The average period of convalescence after operation has been from 3 to 4 months. Most of the workers have returned to their original employment and have not lost time from it since. A number of the patients have failed to increase their weight to their presickness level, but despite this, no increased liability to ill health was noticed. Only 2 patients had abnormal appetites, one being more, and the other less, hungry than normal. When interviewed, the majority were eating normally. The functional result, or the present subjective state of the gastrointestinal tract, was as follows: excellent in 40 per cent, good in 43.2 per cent, improved in 11.4 per cent, and not improved in 3 per cent; in 2.3 per cent of the cases there was a recurrence.

The following features were common to the three cases of recurrence: the patients were all males; the original lesion was a duodenal ulcer; the anastomosis was full width and antecolic; and there was no x-ray or clinical evidence of afferent loop obstruction. These 3 cases support the common belief that duodenal ulcers are more likely to lead to recurrent ulceration, and that free acid is only a predisposing factor to ulceration. All cases of recurrence were of the long loop antecolic type. The recurrence rate therefore was antecolic in 3.3 per cent (92 cases) and retrocolic in 0 per cent (34 cases). One other feature common to all 3 cases with recurrence was a wide stoma. X-ray examination and fractional test meal studies showed that the stomach remnant emptied readily and rapidly. This does not support the view that rapid emptying gives greater protection against recurrent ulceration because of the more rapid neutralization of acid.

There are 3 possible causes for the not uncommon postcibal syndrome of disagreeable sensations on taking food: (1) the small size of the stomach stump, (2) reflux into the afferent jejunal loop, and (3) "dumping" into the jejunum. The author does not consider distention of a small stomach stump or reflux into the afferent loop to be the cause of these symptoms for a number of reasons. In this series only a few patients stated that their meals were of necessity of smaller volume than normal, although many restricted the volume of food in order to lessen the postcibal symptoms. "Dumping" is the commonly accepted cause of most of the unpleasant symptoms after gastrectomy, and the author suggests, as do many others, that a reconstruction of the Hofmeister-Finsterer valve type might help to do away with some of the jejunal dumping by narrowing the entrance to the jejunum. He believes further that rapid emptying of the stomach due to the size of the anastomosis is responsible for the vomiting of bile in some of these patients.

In the course of this study 71 fractional test meals were carried out. Mucus was present in all specimens in all cases. Bile was present in all specimens in most of the cases. All of the patients showed a lowered total acidity, which indicated an actual diminution in the quantity of gastric juice secreted. The cases in which the test meals were done were divisible into two main groups: 49 in which the ulcer, whether gastric or duodenal, was removed completely, and 22 in which the modern modification of pyloric exclusion for duodenal ulcer was performed. The 49 test meals after routine gastrectomy confirmed the usual findings, i.e., most of the cases failed to show the presence of free acid and all showed a diminished total acidity. Only 7 cases showed free acid. In 2 of these the patients had an excellent clinical result, in 4 a good result, and in 1 there was some improvement. The figures show that the stomach remnant does not appear to behave differently whether the ulcer was gastric or duodenal, although duodenal ulcer is usually associated with a much higher acidity. The length of time after operation would appear to make no difference to the acid secreting capabilities of these postoperation stomachs. The 22 test meals after gastrectomy with pyloric exclusion and excision of the antral mucosa showed that 14 of the patients had free acid. If one believes that recurrence of ulceration is at least associated with the presence of free hydrochloric acid, then one might expect that the incidence of recurrence in this group would be higher. Fortunately this seems not to be so, although most of the cases are of fairly recent operation date. The presence of free acid is rather alarming and suggests that until we know more about the exact role of free acid in peptic ulceration, pyloric exclusion should not become a routine operation. The higher incidence of free acid in these cases may be due to incomplete removal of mucosa from the pyloric antrum, or possibly because the whole of the first part of the duodenum is preserved and continues to manufacture gastrin.

Hypochromic anemia is definitely a complication of partial gastrectomy, but does not occur frequently enough for the operation to be condemned on that account. It is more common after gastric ulcer and is almost always of the microcytic type. It is usually of mild degree but may become severe if not treated. In either case response to iron is excellent. Diet for prolonged periods may be a predisposing factor, but

the anemia is not related to the presence or absence of free acid. The anemia is insidious and often causes no complaints, and females are more prone to it than males. A preoperative anemia is not unreversible and the clinical result does not depend upon the blood picture. The possibility of anemia in a patient after a Polya gastrectomy for gastric ulcer should be borne in mind, since it seems to be a disadvantage of that operation. JOHN L. LINDQUIST, M.D.

Aberrant Gastroduodenal Pancreatic Tissue (Les pancréas aberrants gastro-duodénaux). **R. Joyeux, H. L. Guibert, and Guerrier.** *J. chir.* Par., 1947, 63: 261.

The discovery at operation of aberrant pancreatic tissue is not infrequent and such tissue should no longer be considered an anatomical curiosity. The authors present the case histories of 3 patients in whom accessory pancreatic tissue was found, in 1 patient on the duodenal bulb, and in the other two on the wall of the pyloric antrum. The symptomatology closely resembled that of an ulcer and it was with the probable diagnosis of duodenal ulcer in 2 cases and of pyloric ulcer with stenosis in the other case that the patients were operated upon. Subtotal gastrectomy was done in each of the 3 cases.

A review of the literature presents one series of 33 patients exhibiting aberrant pancreatic tissue, all of whom had symptoms which led eventually to surgical intervention. These as well as previous reports bear out the fact that accessory pancreatic tissue occurs most frequently in the stomach, duodenum, and jejunum. The aberrant tissue was found in the wall of the pyloric antrum or the duodenal bulb in 26 of the 33 patients, near the duodenojejunal angle in 2, in Meckel's diverticulum in 2, and in the gall bladder, the ampulla of Vater, and the rectal mucosa in 1 patient each. It is because of the predominant localization in the pyloroduodenal area that symptoms requiring surgical intervention may occur.

Anatomically, the accessory pancreas may be represented as a small plaque, a small tumor, or, more often, by a simple thickening of the wall of the digestive tract which often may cause ulceration of the mucosa. In the usual case the tumor is small and is located either in the submucosa or the muscularis where it separates the muscular fibers. Some of the aberrant tissue may merely rest upon the gastroduodenal wall. Histologically, in the great majority of cases the tissue contains both exocrine and endocrine elements. However, in many cases the cells of the islands of Langerhans and the ductile elements may not only be atrophic, but the site of acute or chronic inflammation or of cystic degeneration.

The aberrant pancreas is physiologically active tissue. Many reports in the world literature associate accessory pancreatic tissue with the presence of gastroduodenal ulcer but in the author's experience this was an uncommon couplet. The mucosa is usually intact and it may be mere coincidence that an ulcer is found in contact with an accessory gland.

The symptoms may be merely functional. Dyspepsia is a common complaint. Symptoms of gastroduodenal ulcer with or without pyloric stenosis are frequent. Two factors in the operative diagnosis are important: (1) the pancreatic nodule has neither the consistency of a neoplasm nor of an ulcer, and (2) the serosa does not have the cicatricial appearance of serosa in contact with an ulcer.

The accessory pancreatic tissue results from the faulty fusion of the buds which embryologically form the pancreas. Some workers are of the opinion that the occurrence is a throwback to the lower animals, the cyclostomes, in which the pancreas is included in the intestinal wall.

When symptoms indicate laparotomy and suspicious nodulations are found in the upper intestinal tract, excision of the nodule and immediate frozen section examination will determine the diagnosis in the majority of cases. Simple excision of the lesion is adequate in most cases but partial gastroduodenectomy may be necessary when a large amount of accessory pancreatic tissue is complicated or associated with peptic ulcer. ORVILLE F. GRIMES, M.D.

Schwannomas of the Stomach (Sur le schwannome de l'estomac). **Jean Gomez.** *J. chir.*, Par., 1947, 63: 463.

The frequency with which schwannomas of the stomach occur, as reported in the world literature, varies between 0.5 and 1.5 per cent of all gastric tumors. The schwannoma (more familiarly known in the American literature as neurilemmoma or perineural fibroblastoma) is the second most common benign gastric tumor, the myoma being the most common.

Various opinions have been expressed concerning the origin of these tumors. It is the belief of some that they arise from the endoneurium and are therefore of mesodermal origin. Others have indicated that they arise from the cells of Schwann and hence from ectodermal anlage.

The favorite sites are the pylorus and the cardia. Clinical symptoms arise from the mechanical interference occasioned by the presence of the tumor. These forms are described: (1) an interstitial form in which the tumor is entirely intramural, ovoid, usually small, seldom ulcerated, and well limited by a connective tissue capsule; (2) the endogastric or pedunculated form which may become quite large and is usually ulcerated; and (3) the extragastric form arising from the serosa which may attain a large size and may displace the stomach considerably by its pressure.

Of especial interest is the usual existence of submucosal nodules separate from the principal tumor but having an identical histological picture. The tumors are extremely pleomorphic, frequently assuming fibrosarcomatous or myosarcomatous aspects. Pseudocaseous or colloidocystic degeneration is common and it is for these reasons that the malignancy or benignancy of these tumors is many times in doubt.

Gastric hemorrhage, occasionally of sufficient severity to cause an anemic state, is the most common clinical finding. Vague dyspepsia is common.

Roentgenologically, by the use of contrast media, the pedicle of the tumor can many times be shown; this will indicate a benign process in most cases. The mobility of the lesion is the important clinical factor in distinguishing the benign lesions from cancerous growths.

One can entertain a presumptive diagnosis of a benign gastric tumor by the discovery of an epigastric mass with the preservation of a state of well-being, gastric hemorrhage without pain, the existence of a hemorrhagic state without cachexia, and the absence of periodicity of the pain. These clinical findings plus the roentgenological findings of a perfectly delimited tumor with regular contours and an ulceration in the mass, and a gastroscopic appearance similar to that of a diverticulum may permit one to make a presumptive diagnosis of schwannoma.

If untreated, these tumors may cause distress by compression of the neighboring organs, hemorrhage, infection, obstruction at the pylorus, perforation, or by malignant degeneration.

The treatment should always be surgical. Local excision of the lesion with a generous margin of the base is employed many times. However, the authors believe that subtotal gastrectomy by which no less than two-thirds of the stomach is removed is the method of choice in order to remove the aberrant nodules which are usually present. A limited excision may be employed for the extragastric type.

The author briefly presents the case histories of 4 patients in whom subtotal gastrectomy was performed to remove endogastric schwannomas. All have remained well. ORVILLE F. GRIMES, M.D.

Gastric Cancer. Owen H. Wangensteen. *J. Am. M. Ass.*, 1947, 134: 1161.

This extensive review of the problem of gastric cancer deals with the disease from the standpoint of etiology, diagnosis, and treatment. It is of especial interest, since it combines scientific data with philosophic thinking and a delineation of the problems facing us at present and in the future.

The ultimate salvage of life following a diagnosis of gastric cancer is small. Though gastric cancer is curable, the disease is rarely recognized in time for such a cure to be accomplished. Cancer of the stomach is the most frequent of all malignant growths.

From the standpoint of etiology, there is a wide diversity of opinion concerning the origin of gastric cancer. Most authorities agree that gastric cancer probably does not originate *de novo* from a normal gastric mucous membrane. There is no unanimity of opinion, however, concerning the importance of items which it is believed may give special encouragement to the development of gastric cancer; among these are to be enumerated: (1) the benign polyp, (2) atrophic gastritis, and (3) gastric ulcer.

There is also a sharp difference of opinion in regard to the role of extrinsic factors in the origin of gastric cancer in man. There are those who believe that the so-called constitutional susceptibility is important. Nettleship included such extrinsic factors as diet, age, heredity, heat, alcohol, bacteria, viruses, allergy, and infections. A study carried out in the author's clinic indicated that approximately 30 per cent of families give a history of cancer sufferers among their members, but there was no closer correlation than this.

Several well known surgeons who, in the estimation of their colleagues, were authorities on the clinical aspects of the disease and who essayed to instruct others in the early manifestations of gastric cancer recognized the signs of the disease in themselves too late to benefit by that therapeutic agent of which they themselves were masters. Among them are to be enumerated the names of Johannes von Mikulicz, W. J. Mayo, D. P. D. Wilkie, and Martin Kirschner. R. D. Carman, a well known roentgenologist who contributed a useful sign to the roentgenologic diagnosis of gastric cancer, had a gastric cancer which was inoperable before he recognized the signs of the disease in himself.

In an attempt to find precursors of gastric cancer, an experiment was undertaken to scrutinize carefully all patients with demonstrated histamine achlorhydria in men over 55 and in women over 65 years of age. Among 464 patients who were achlorhydric to histamine, 15 patients with polyps were found—the most fruitful observations of the study. During the 15 month period that this study was under way, only 3 undetected gastric carcinomas were uncovered. Only 1 of these, however, was early. This patient's lesion was missed by roentgen examination. At operation it was found that he not only had a gastric carcinoma but also a second primary lesion of the cecum.

The experience of this clinic suggests that radical operations for gastric cancer, including total gastrectomy, can be performed at a reasonable risk. For the past 4 years, during which time 160 resections (including total gastrectomies) were performed, the hospital mortality was 8.1 per cent. In 1945 there were 62 resections (including 9 total gastrectomies) with 3 deaths (4.8 per cent mortality). The resection rate of patients operated upon for gastric cancer in this clinic was approximately 90 per cent. This implies that palliative resections were undertaken in a number of instances.

Cancers *in situ* perhaps will not often be recognized in the stomach; yet periodic examination of all men and women who have reached the "cancer years" undoubtedly will make an important contribution to the earlier recognition of cancer. One cannot await the complete evolution of the clinical symptoms.

The establishment of cancer detection clinics, staffed by specialists, affords the best promise of the early recognition of cancer. Women over 40 and men past 50 years of age should report regularly to such clinics. The solution of a difficult problem such as this demands the following: (1) members of the

medical profession must look at the problem realistically and learn to know all the facts bearing on it; (2) they must constantly enlarge their knowledge of the field by vigorous research and clinical investigation; (3) all available resources must be combined to lend pursuit of the inquiry the greatest promise of solution; (4) the solution of the problem must envisage an interest in the problem as it relates to the present generation as well as to those yet unborn.

New discoveries as a result of a co-ordinated and energetic research program constitute the hope of the future. HAROLD LAUFMAN, M.D.

A Statistical Study of 1,405 Cases of Cancer of the Stomach. W. L. Harnett. *Brit. J. Surg.*, 1947, 34: 379.

This study is based on the statistical survey of 1,405 cases of primary carcinoma of the stomach published by the British Empire Cancer Campaign in 1944. The cases were followed up for 5 years, with only 1 per cent of the patients being untraced.

There were 856 males (11.7 per cent of all male cases of cancer registered) and 549 females (6.9 per cent of all female cases). The region of the stomach affected was known in 871 cases by operation or postmortem findings. Fifty-four per cent of the carcinomas were in the pyloric region, 33 per cent in the midgastric region, and 13 per cent in the cardiac region.

The youngest patients were a female aged 20 and a male aged 21. The mean age of the 691 patients who were submitted to operation was 56.83 years.

The occupations of the male patients were arranged in order of frequency and compared with the percentage of males over 14 years in Greater London following the same occupations. The figures warranted the conclusion that those admitted were a fair sample of the general population and, thus, there was no connection between the occurrence of gastric carcinoma and any of the occupations.

Definite pain following eating was the first symptom in 24.7 per cent of all the patients. Sudden onset with the vomiting of blood occurred in 1.5 per cent of the entire group and in 3.5 per cent of those with growths in the cardiac region. In 0.6 per cent there were no symptoms directly related to the stomach and the diagnosis was established by surgery or autopsy. In 1.3 per cent, metastases to the bones, lungs, or the lymph nodes preceded discovery of the primary tumor. Onset of the symptoms was stated to be gradual in 68.4 per cent and sudden in 22.8 per cent.

Fifty-four and one-half per cent of all the patients consulted a doctor within the first 3 months, and 10 per cent within the next 3 months. There was some delay on the part of the physicians to treat the patients. Sixteen per cent came to the hospital directly; 37 per cent were referred to the hospital for investigation at once, and 13 per cent after an interval of less than 3 months; 19 per cent were treated symptomatically for more than 3 months, and 1 per cent were told not to worry.

Seventeen and one-half per cent of the patients lost up to 28 pounds in weight and 19.4 per cent lost more than 28 pounds. Only 3.8 per cent lost no weight at all and the amount lost in the other cases is not known. There was a definite palpable tumor in 49 per cent of the patients and an indefinite mass in 9 per cent. Obstruction to the passage of food was diagnosed clinically in 33.6 per cent of the growths in the pyloric region, in 10 per cent of those in the midgastric region, and in 7 per cent of those at the cardia. Recognizable distant metastases were present in 32.5 per cent of all the patients on admission to the hospital. In 6.9 per cent the cervical or supraclavicular lymph nodes were affected, and in 5.4 per cent metastases could be palpated on rectal examination. Of 457 recognizable metastases, 85.3 per cent were in the liver or abdominal organs, 3.5 per cent in the lungs, and 3.6 per cent in the bones.

The 1,405 patients diagnosed as having gastric carcinoma were treated as follows: 681 had neither surgery nor radiotherapy; 33 were treated with radiotherapy; 243 had their stomachs resected; 215 had a palliative procedure, and 233 were explored only. The operative mortality for all radical operations averaged 32.9 per cent, ranging from 25.4 per cent for the Polya method of partial gastrectomy to 90 per cent for total gastrectomy. The 5 year survival rate for males for all radical operations was 19.8 per cent, and for females 27.1 per cent, not including the operative mortality. The 5 year survival rate for males for all methods of resection was 28.6 per cent and for females, 29.8 per cent, not including the operative mortality.

There were 56 patients surviving after 5 years (4.03 per cent of all cases). Of these, 36 had been treated by partial gastrectomy, 7 by palliative operations, 2 by radiotherapy, 1 had exploration only, and 10 had not been treated. The proper diagnosis of the latter 10 has since been questioned.

DANIEL RUGE, M.D.

Irradiation of Gastric Cancer. G. Cranston Fairchild and Alan Shorter. *Brit. M. J.*, 1947, 2: 243.

Cancer of the stomach still remains a problem. It is responsible for 13,000 deaths annually in Great Britain, and for 40,000 in the United States, 33 per cent of all cancer deaths in America. It is the commonest type of cancer, with the poorest results from treatment, for, on the average, only from 1 to 4 per cent of all patients are alive after 5 years following curative surgery, and only about 4 months' prolongation of life can be obtained by palliative operations. At present some 80 per cent of patients with gastric cancer are beyond any hope of cure by surgery alone when first brought to the surgeon. But what of irradiation—for postmortem findings show that over 20 per cent of people dying of gastric cancer have the disease still confined to the stomach and immediately adjacent lymph glands. Because of the impossibility of a surgical cure in such a vast number of cases, many other forms of treatment, including irradiation, have been tried, but without striking success.

Different forms and combinations of irradiation applied to this viscus have their limitations and shortcomings. External irradiation fails because of the deep situation of the gastric tumour and its close relation to other vital organs—both factors tending to prevent adequate tumor dosage—and because of the high but variable radioresistance of gastric cancer cells, possibly increased by infection. Movements of the tumor make accurate centering of the x-ray beam at repeated exposures difficult to obtain. Contact therapy with the Chaoul tube covers a relatively small area (2 cm. in diameter) in each field, with very little penetration at low voltage. With the Chaoul tube, bulky tumors could not be destroyed by single surface doses at one operation, but needed repeated exposures. This could be done only through some kind of fistula or pouch formation. With such a small field as 2 cm., repeated applications would be required for most inoperable tumors, with the obvious difficulty of adequate and uniform dosage. Also, such localized irradiation would have no appreciable effect on any glandular or other local spread, the presence of which is the usual reason for inoperability. Radon seed implantation has the same difficulty of uniform and adequate dosage (as shown by subsequent radiography) when introduced at operation from either serous or mucous surface, or through a gastrostomy opening or the esophagoscope. There are also dangers of hemorrhage and infection and perhaps perforation due to massive necrosis of the tumor, while the adjacent field of spread does not receive adequate irradiation.

Intracavity irradiation with the five-way tube described by Livingston and Pack (1941) has, they claim, the advantages of easy application, fractionation of doses, avoidance of damage to adjacent vital organs, freedom from dangers of hemorrhage, infection, and perforation, and no interference with food intake, but they had not at that time determined how effective a total dose patients would stand, the most effective fractions into which to divide the total dose, or the results as regards palliation or cure. Used alone it would appear not to have much effect on local spread, but combined with direct irradiation it might perhaps be used to supplement the dose reaching the center of large gastric tumors. Many people think that irradiation not only shortens the patient's life but also adds to his sufferings, and therefore is quite unjustifiable. While this may be true of many of the other methods of treatment, direct irradiation at high intensity has none of these disadvantages.

Fairchild (1935) first conceived the idea of direct irradiation of deep-seated tumors exposed temporarily at operation. The following advantages of the method are noted.

1. More accurate information about the size, shape, position, and extent of the primary lesion, and any local or general spread, can be obtained at the exploratory operation than can be found out by any other methods, either clinical or laboratory. In the thorax, where a fairly satisfactory radiological examination can usually be made, the extent of a cancer is almost invariably greater than it would seem from x-ray films. So, in the abdomen, the growth is nearly always more extensive than can be determined by the usual examinations and investigations. According to Walters et al. (1942), exploratory operation is the only reliable way of deciding the correct form of treatment.

2. Biopsy specimens can usually be obtained to help confirm the diagnosis. With palpable glandular involvement this can be done safely, but incision of the tumor may spread tumor cells or lead to perforation owing to subsequent massive irradiation. Thus biopsy may not be practicable in all cases, but being able to see and feel the tumor should make the diagnosis more certain than when relying on external methods of examination alone.

3. A more accurate and effective dose of irradiation at high intensity can be given direct to the tumor and field of local spread without irradiating such a large volume of normal tissue, including vital organs and skin, unavoidable when irradiating from the skin surface. This may be of great importance in an already anemic and cachectic patient.

4. More accurate centering of the x-ray beam is possible under direct vision than when relying on x-ray films or clinical examination alone.

5. The skin is left practically intact, and will permit further full dosage to be given externally at a later date should this be deemed necessary. Supplementary external irradiation was given later in some of the earlier cases, beginning about 10 days after operation, as it was believed the initial dose was too small to cure. Some patients had further external irradiation after some months.

6. Various operations to relieve obstruction can be performed before the irradiation, at the same or an earlier and less extensive laparotomy, such as gastrostomy for cardiac obstruction and gastrojejunostomy for pyloric lesions. Though the obstruction may not be severe it increases owing to fibrosis of the tumor after irradiation. In hopeless cases these operations can be done without irradiation to relieve symptoms.

Diagnosis and localization of the tumor are achieved as accurately as possible by clinical, radiological, gastroscopic, esophagoscopic, and laboratory investigations. The general condition of the patient is investigated as regards the possibility of metastases, state of nutrition, and fitness for anesthesia and operation.

Owing to the tendency of the growth to spread along the stomach, or to lymphatics above, behind, or below the stomach, the exposure must be such as to enable the direct irradiation to be carried out in an anteroposterior plane; otherwise uniform irradiation of the tumor area would not be possible. It follows that the left transthoracic approach is unsuitable for direct irradiation even for the cardiac area and lower esophagus. This may be in one or two stages (Fairchild and Shorter, 1945):

1. When there is well marked cardiac or pyloric obstruction gastrostomy, gastrojejunostomy, or even

jejunostomy may be necessary before the patient's condition can be improved sufficiently to stand the wider exposure and irradiation. This is usually done through a small upper left paramedian incision making exploration of the tumor and the whole abdomen possible. Many cases have in this way been found unsuitable for irradiation owing to unsuspected widespread metastases.

2. When the patient's condition seems satisfactory the abdomen is explored through a different incision more suitable for extension, even into the thorax if necessary. This practice has been followed when the condition of the patient will allow it, so as to avoid the two operations advocated by Garlock. Also it saves moving the patient in making separate incisions for the exploration and the main exposure.

The form of treatment to be carried out cannot be decided upon beforehand, so preparation must be made for all contingencies so far as is possible. The abdomen must be thoroughly explored before making an extensive exposure, especially before opening the thorax. It would seem to be unwise, and unfair to the patient, to open his thorax and divide his diaphragm before estimating carefully the extent of spread in the abdomen.

When operations to relieve obstruction are necessary they are done before the irradiation, and, when possible, in an area of the stomach not to be irradiated. Irradiation of normal viscera, so far as possible, is avoided by displacement and packing out of the field. In earlier cases lead screening was used to protect the skin edges of the wound. More recently a special sterilized applicator was introduced into the wound. Sterilized oiled silk protects the field against infection during irradiation but allows accurate visual centering of the tumor in the x-ray beam. To avoid shock produced by frequent moving, a special trolley has been designed on which the patient can have both the operation and the irradiation.

Fifteen patients were treated by direct irradiation. These cases can be divided into two groups. In the first group were 7 cases in which the irradiation was purely palliative owing to obvious spread beyond the possible field of irradiation, or to a poor general condition. Of these, 1 patient is alive and well after 5 weeks; 1 lived 6 months, 1 lived 5 months, and 2 lived 4 months; the rest died sooner. In the second group of 8 cases the growth appeared to be limited to an area that could be irradiated. Of these, 1 patient lived 24 months, 2 patients lived 15 months, 1 lived 7 months, 1 lived 4 months, and 1 lived 3 months after treatment. The remaining 2 patients died within the first week—one from bilateral pulmonary collapse while the wound was being closed, the other from spontaneous pneumothorax on the opposite side 4 days after operation.

Although the series is small, direct irradiation at high intensity will prove to be a rational and hopeful advance in the treatment of cancer of the stomach and other viscera. Whether the cancer is rendered inoperable by the poor general condition of the patient or by irremovable local spread, this method will often succeed where surgery alone must inevitably fail. Though wider exposure is needed than for surgery alone, with adequate precautions the whole procedure should not be so shockproducing as is wide surgical excision.

Exploratory operation is the only reliable way of deciding the correct form of treatment, and the hospital of the future will have a radiotherapy room adjoining the operation theater to facilitate direct irradiation. CHARLES BARON, M.D.

Perforated Sigmoiditis (Sigmoiditis perforada). **Adolfo Dujovich and S. Form.** *Brasil méd.-cir.*, 1946, 8: 257.

The authors present the case of a patient with perforated sigmoiditis who was operated on 6 hours after the perforation. In this case it was not possible to identify the etiological agent, although other authors found the ameba to be the causative factor in the majority of cases.

A relatively large ulceration of the mucosa and submucosa was encountered with an abundant infiltration of leucocytes, as well as an increased number of histiocytes and of other elements not well identified.

The symptomatology was similar to that of an acute perforated appendicitis. Pain, usually in the left lower hypogastric area, was sudden in onset and unbearable, being similar to the type found in gastroduodenal ulcer, and it produced a certain amount of shock. The patient was in a cold perspiration and fainted at the height of the paroxysm. At the onset of the peritonitis the pulse and temperature were parallel. Tenderness was illicited on the side of the perforation, associated with muscular rigidity which was more prevalent on the left side. Abdominal distention came later. Vomiting was not early or frequent although nausea was present from the start.

This condition must be differentiated from acute appendicitis, perforated gastric and duodenal ulcers, and intestinal obstruction.

The prognosis depends on early surgical intervention, virulence of the micro-organisms, and the impossibility of the peritoneum to form protective adhesions. The author's patient was discharged in 12 days after admittance.

The treatment was simply surgical, and consisted of suture of the defect in 3 planes and covering of the site of perforation with epiploicae. Sulfa therapy with drainage of the peritoneal cavity is of unquestionable value. ARTHUR F. CIPOLLA, M.D.

A Case of Multiple, Hyperplastic Tuberculosis of the Colon. Harald Brodin. *Acta radiol.*, Stockh., 1947, 28: 227.

Hyperplastic tuberculosis of the intestine is, as a rule, a solitary tumor, most often located at the ileocecal valve. It is an uncommon condition. In the literature one series of 72 cecal tumors is reported, 9 of which were tuberculous, and of the 9 only 5 were of the hyperplastic form. Another report of 8,087 autopsies showed 233 cases of intestinal tuberculosis of which 2 were of the hyperplastic

type. Cases in which multiple hyperplastic tuberculous lesions of the intestinal tract are present are rare.

In patients suffering from this disease other foci of tuberculosis are uncommon. Some authors believe this form of tuberculous infection is a primary type of infection. The mode of infection is thought to be via the blood stream, although it may originate by lymphatic spread from tuberculous mesenteric glands.

The symptoms of hyperplastic tuberculous infection of the colon are usually of long duration and consist of colicky pain, loss of weight, nausea, and anorexia. Diarrhea, constipation, or alternating periods of each may be present. Examination usually reveals a palpable abdominal tumor, anemia, slight rise in temperature and a raised sedimentation rate. Fistulas may be present. The diagnosis is difficult, and the differentiation from cancer may be impossible. Multiple cancer of the colon is more common than multiple hyperplastic tubercular tumors. A case of multiple hyperplastic tubercular tumors of the colon is presented.

F. J. LESEMANN, JR., M.D.

The Management of Cancer of the Colon. Paul I. Hoxworth and James Mithoefer. *Surgery*, 1947, 22: 271.

The present differences of opinion among surgeons with respect to operative procedures for cancer of the colon lie largely in the technique of resection and reestablishment of continuity of the bowel after resection. Two schools of thought exist—one chooses a method requiring delayed anastomosis and the other prefers to restore continuity of the intestine immediately. Much progress has been made along both lines of approach since cure of cancer of the colon was first undertaken. At the authors' clinic the plan of choice has been that of anastomosis at the time of resection by either an open or closed method. For the success of this procedure it is necessary to establish suitable conditions for the relief of obstruction, for the avoidance of sepsis, and for primary healing by use of careful preoperative, operative and postoperative measures. If these conditions cannot be met in each individual case, it is safer to resort to exteriorization and delayed anastomosis. Under this plan, 87 resections for cancer of the colon were performed in the 9 year period from 1938 to 1946. The management is presented in some detail and the operative results are reported.

Emphasis is placed upon the following fundamental principles:

In the preparation of the patient for resection, relief of obstruction and thorough cleansing of the intestine should be achieved, along with preliminary correction of anemia and of disturbances in chemistry, nutrition, and hydration. Operative principles include the use of the transverse abdominal incision, careful attention during resection of the mesentery to preservation of the blood supply to the segments of bowel at and adjacent to the proposed site of anastomosis, gentleness in the dissection and handling of the bowel and its mesentery, adequate mobilization of the segments to be anastomosed in order to prevent tension at the line of suture, precision in the placing of sutures after careful preparation of the bowel to receive them, the use of inverting mattress sutures which catch the submucosa but do not penetrate the mucosa and are tied tightly enough to hold serosal surfaces in apposition without strangulation of the tissue, avoidapce of inverting too much of a diaphragm, accuracy in approximating the edges of the mesentery and in reperitonealizing denuded areas, isolation of the field of resection, and exclusion of contaminated gauze, instruments, towels, and gloves from the field before reperitonealization and closure of the wound.

Further principles include the use of continuous gastric aspiration until obstruction is relieved, and, during the immediate preoperative and postoperative period, the provision of adequate hydration and nutrition, the prevention of atelectasis after operation, and parenteral administration of sulfadiazine and penicillin if soiling has occurred or at the onset of signs of sepsis.

The 87 cases represent an operability rate of 60.4 per cent among a total of 144 cases. Of the 87 resections performed, 16 were classed as palliative. In lesions of the right colon, ileotransverse colostomy was carried out as the first procedure in 12 cases, in 10 of which it was only palliative and was not followed by resection. Only 3 of the 24 patients with cancer of the right colon who had resection showed obstruction, whereas about half of those with tumors of the transverse and left colon had complete or partial obstruction at the time of admission to the hospital. In all of these cecostomy or transverse colostomy was done as a preliminary step to relieve obstruction. In 6 of 63 cases in which resection was done for lesions beyond the hepatic flexure, circumstances encountered at the time of resection prevented the operator from proceeding with end-to-end anastomosis.

Among the 87 cases of resection there were 6 deaths, a mortality rate of 6.9 per cent. Four deaths were due to leakage at the site of the anastomosis which resulted in peritonitis. All of these cancers were in the left colon. One patient died of pneumonia and 1 of uremia. The average hospital period for the 79 surviving patients treated by resection and immediate anastomosis was 26 days from the time of resection to time of discharge from the hospital. In patients in whom a cecostomy was performed, the average interval between the cecostomy and resection was 15 days.

JOHN L. LINDQUIST, M.D.

The Management of Carcinoma in the Several Parts of the Colon. William F. MacFee. *Ann. Surg.*, 1947, 126: 125.

The author describes the historical development of the modern techniques used in surgical therapy of carcinoma of the colon. He cites the perfection of an aseptic method of resection and anastomosis, prox-

imal decompression in the presence of the obstruction, the use of intestinal antiseptics, earlier diagnosis and greater appreciation of the importance of fluid and protein balance, and the use of vitamins and blood transfusion as factors in lowering the mortality resulting from the surgical treatment of carcinoma of the colon.

The various proponents of the exteriorizing stage resections and those advising primary resection with end-to-end anastomosis are named. The author states that the present trend is in favor of resection with end-to-end anastomosis, and justifies this by stating the fact that in the numerous series of case reports, the mortality of primary resection with anatomical anastomosis is half that of exteriorization with stage resection.

Reichel's basic principles for closed resection with anastomosis are reiterated, i.e., the general condition of the patient must be adequate for a long operation, the proximal bowel must be decompressed, the intestine must be viable and free of circulatory disturbance, and there must be no tension on the sutured lines of the anastomosis. In the absence of obstruction, fixation, or infection a carcinoma in almost any part of the colon may be resected and continuity restored immediately without undue risk.

Uncomplicated carcinoma of the cecum, ascending colon, and hepatic flexure may be resected and ileotransverse colostomy performed at a single operation. In the presence of obstruction, fixation, or infection, ileotransverse colostomy should be done first with resection following later.

Carcinoma of the transverse colon ordinarily may be resected and anastomosis established as a one stage operation. Obstruction, extensive fixation, or infection calls for preliminary cecostomy.

Carcinoma of the splenic flexure is often recognized late, complications are frequent, and surgical approach may be difficult. Preliminary cecostomy or transverse colostomy should be the rule, with primary one stage resection reserved for the exceptional case. Transverse or subcostal incision provides a good exposure.

In the descending and sigmoid colon, primary resection and immediate anastomosis are permissible provided there are no complications. Obstruction, fixation, or gross infection requires proximal drainage by cecostomy or transverse colostomy, preferably the latter. Diverticulosis may confuse the diagnosis and treatment.

At the rectosigmoid level, preliminary transverse colostomy with complete diversion of the feces is a prerequisite for resection with immediate anastomosis. Faulty healing of the suture line frequently results in leakage, infection, and fistulas. The presence of feces in such a field is a serious disadvantage.

The space about an anastomosis established below the level of the pelvic peritoneal floor should be freely drained through the coccygeal bed. Primary one stage resection and anastomosis may succeed in any part of the colon proper, but it should not be performed for tumors in the rectosigmoid, and its use elsewhere should be restricted to uncomplicated lesions. ERNEST D. BLOOMENTHAL, M.D.

LIVER, GALL BLADDER, PANCREAS, AND SPLEEN

Traumatic Rupture of the Liver without Penetrating Wounds: A Study of 32 Cases. Louis T. Wright, Aaron Prigot, and Lyndon M. Hill, Jr. *Arch. Surg.*, 1947, 54: 613.

This article is a report of 32 cases of traumatic rupture of the liver without penetrating wounds studied at the Harlem Hospital between 1935 and 1946.

Of some 20,000 patients admitted to the Traumatic Service, 18 had subcutaneous rupture of the liver, an incidence of 1 to 1,111. In the present series there were 27 cases among 34,000 admissions, an incidence of 1 to 1,259. These figures tend to show that this condition is not as infrequent as the reports in the literature would lead one to believe.

The liver and spleen together make up 72 per cent of all intra-abdominal injuries of solid viscera, with a somewhat greater frequency of the liver injuries.

Being struck by an automobile and falling are the more common causes of injury. Twenty-one cases occurred in males and 11 in females.

The friability and position of the liver combine to render it vulnerable to direct injury and injury by contrecoup. The larger less protected right lobe is more easily injured. It was injured in 27 cases, the left lobe was injured in 2, and both lobes were injured in 3 cases.

The liver when injured tends to split and crack in stellate fashion with hemorrhage and escape of bile. The dome of the liver was most susceptible which tended to disprove the idea that most ruptures occur along the posterior inferior surface where the liver is thrown against the vertebral column.

In all cases there were moderate (from 200 to 500 c.c.) or larger amounts of blood in the peritoneal cavity. The reasons for this copious hemorrhage are that (1) thin walled hepatic veins have no valves and do not retract or contract; (2) blood mixed with bile does not clot readily; (3) diaphragmatic movements aggravate the injury; and (4) the friable hepatic tissue does not act as a tampon.

More trauma is necessary to rupture the liver than the spleen. In only 10 cases were there no associated lesions. The most common associated injuries were lacerations of the brain and spinal cord, ruptured spleen, and fractures.

In classifying traumatic rupture of the liver the authors favor a classification dependent on the rate of hemorrhage. This rate may not be in proportion to the amount of damage to the liver. In a series of 21 cases reported by Vance, one-third of the patients died at the site of the injury, 38 per cent died within 6 hours, and 28 per cent lived long enough for clinical study.

The authors' 4 clinical types are: (1) massive hemorrhage causing almost immediate or sudden

death, (2) acute hemorrhage producing shortly after injury a state of shock which rapidly becomes deeper, (3) repeated small hemorrhages, and (4) spontaneous cure. Case histories illustrating each type are given. The greatest number of cases fall in the second and third groups.

The diagnosis of rupture of the liver is difficult even without complications. Symptoms may not develop for 6 hours or more. The signs are hemorrhage, shock, and peritoneal and diaphragmatic irritation. Rarely a tender mass may be palpable or blood appears in the vomitus.

Severe abdominal pain made worse with respiration is the most common complaint. Pain radiating to the right or left shoulder (Kehr's sign) is helpful, if present, but frequently it is absent. Vomiting occurs not infrequently as a reaction to the trauma. Symptoms of internal concealed hemorrhage are present.

These cases usually show signs of shock. Bradycardia was not observed. The point of maximum tenderness is apt to be misleading in localizing the lesion. Rigidity and rebound tenderness may be present. A palpable abdominal mass is helpful when present. Jaundice is rare but may appear in from 48 to 72 hours after injury.

Repeated blood counts and hematocrit determinations are necessary until the diagnosis of intra-abdominal injury is established. If blood is found in the urine, it is wise to rule out other causes of concealed hemorrhage.

X-rays may show a high diaphragm on the right in rupture of the liver. Abdominal tap and peritoneoscopy are invaluable aids in diagnosis of rupture of the abdominal viscera. The abdominal tap performed in all 4 quadrants should always be used in any suspected case. It was used in 15 cases and failed to disclose blood in 3. The finding of blood is indicative of intra-abdominal injury, whereas failure to find it does not rule out intra-abdominal injury. No "false positive" results were obtained. Peritoneoscopy was used once with a positive result.

Nonsurgical conditions, such as contusion of the abdominal wall or fracture of ribs with shock due to hemorrhage into cavities other than the peritoneum, must be excluded.

The treatment of this emergency is surgical and delay increases the operative risk. Conservative treatment has a mortality between 75 and 96 per cent. Preoperatively, shock must be combated with blood and plasma. Preoperative enemas and spinal anesthesia are to be avoided. The authors do not use autotransfusion because the blood may be mixed with bile and it may contain toxic products from autolysis of liver tissue.

All cases of suspected liver injury should be explored as bile may be spilled into the abdomen and lead to bile peritonitis, necrotic pieces of liver tissue may be present, or hemorrhage may be uncontrolled. This exploration should be carried out as soon as the diagnosis is made, and supporting measures can be carried on simultaneously. Early operation tends to eliminate complications such as infection and fatty and hepatic tissue embolism.

Bleeding may be controlled by steam cautery, compression clamps, large sutures with bone plates or omental and fascial strips, digital compression of the hepatic artery, or suture of the liver to the abdominal wall. Various types of gauze packs or muscle, omentum, fat, or rubber dams have been used. Simple tears can safely be sutured. Recent work with gelatin sponge indicates that it may be the best method of repair as it reduces operating time, loss of blood, and mortality rates.

The prognosis for rupture of the liver depends on the severity of the rupture but also on the severity of the associated lesions. Only 6 of the 32 patients in this series lived—a mortality of 81.3 per cent. Of the 26 who died, 11 died within 4 hours without surgical intervention. Of the 15 operated on, 9 died—an operative mortality of 60 per cent. Of the 6 who lived there were only 2 with associated injuries. In all cases the rupture of the liver was packed with gauze. The only complications were purulent discharge from around the packing and a decubitus ulcer in 1 case. No instances of hepatorenal syndrome or liver death were encountered. In the recovered patients the morbidity varied from 16 to 98 days. The gauze packing was removed between the fourteenth and fortieth days. ROBERT R. BIGELOW, M.D.

Congenital Absence of the Gall Bladder. Earl O. Latimer, F. L. Mendez, Jr., and W. J. Hage. *Ann. Surg.*, 1947, 126: 229.

Three cases of congenital absence of the gall bladder discovered at operation are presented. In 1 of these cases a cholangiogram, made postoperatively by means of a T-tube, showed the common duct to be patent but revealed no evidence of structures resembling either the cystic duct or the gall bladder. Oral cholecystography also failed to show evidence of an intrahepatic gall bladder. An analysis of 71 cases of congenital absence of the gall bladder, approximately half of which were found at operation and half at autopsy, is tabulated with respect to age and sex, symptoms, preoperative diagnosis, and attempts to prove the presence of an intrahepatic gall bladder. Syphilis, catarrhal inflammation of the biliary tract, fetal peritonitis, maternal toxins, and mechanical factors have been advanced by various authors as the causes of this anomaly. A more easily defended theory involves the embryology of the biliary tree.

There is no group of symptoms or signs which is of value in making the diagnosis preoperatively. When cholecystography fails to produce any shadow whatsoever, congenital absence of the gall bladder is not suspected because of its rarity. There is no reported case in which the diagnosis was made before operation or autopsy. Should surgical procedure fail to reveal the gall bladder in or about its normal location, the presence of an intrahepatic gall bladder should be ruled out, preferably by retrograde cholangiography. JOHN L. LINDQUIST, M.D.

The Diagnosis of Pancreatic Disease by Enzyme Tests. Lester M. Morrison. *J. Lab. Clin. M.*, 1947, 32: 1107.

The clinician has long found the diagnosis and treatment of diseases of the pancreas to be most difficult and uncertain.

The 20 patients with organic disease listed included 3 patients with carcinoma of the pancreas, 2 with pancreatic cirrhosis, 3 with cirrhosis of the liver, 3 with duodenal ulcer, and 1 each with gastric ulcer, infectious hepatitis and cholangitis, carcinoma of the pyloric end of the stomach, carcinoma of the gall bladder and bile ducts, and nontropical sprue, respectively.

The respective average readings in the "normal" controls and the "functional" cases appear to be clearly defined. However, the difference between the average readings of the "functional" and those of the "organic" diseases seems small. This lack of contrast appears to be due to the inclusion of a group of cases under "organic" causes in which the pancreas itself was not primarily involved. Cases of gastric and duodenal ulcer or cholelithiasis are examples. On the other hand, when the cases in which the pancreas is involved primarily, such as by carcinoma or cirrhosis or by stone, are examined, the test readings are consistently zero or very close to zero.

Percentages were not calculated since the range of variation in normal subjects, patients with organic disease of the upper digestive tract, and patients with functional diseases of the upper digestive tract were so great that only repeated zero or near zero readings were of diagnostic significance.

Over 1,000 pancreatic enzyme tests were made of the duodenal secretions in a group of normal subjects, in a group of patients with "functional" or nonorganic disease of the upper digestive tract, and in a group of patients with organic disease of the pancreas, biliary tract, stomach, or duodenum.

The range and mean of duodenal pancreatic enzyme tests for normal subjects and patients suffering from upper digestive tract disorders are described. Variations of test findings are very wide in both normal subjects and patients with most organic diseases of the pancreas or upper digestive tract.

Normal subjects as well as patients with extensive and severe pathologic involvement of the pancreas such as cancer may give zero or near zero test readings in individual duodenal pancreatic enzyme tests.

In patients with organic disease of the stomach or biliary tract, pancreatic duodenal enzyme tests revealed no individual distinctive or diagnostic findings. However, their group mean value was definitely lower than the comparable value in normal subjects.

A group of 10 patients with chronic low grade or moderate inflammation of the pancreas, as revealed at operation, underwent a series of duodenal pancreatic enzyme tests performed before and after operation. The duodenal enzyme study failed to show any consistently abnormal findings of diagnostic value either preoperatively or postoperatively.

In 6 cases of extensive involvement of the pancreas by cancer or cirrhosis with pancreatic lithiasis, 125 tests gave abnormal findings in the duodenal pancreatic enzyme tests. These abnormal findings showed either zero or near zero values.

If a zero reading was found in the pancreatic enzyme tests of a normal subject, it was not consistently found at subsequent determinations. In the presence of advanced and extensive pancreatic disease, such as cancer or cirrhosis, zero and near zero readings were found consistently at all subsequent determinations.

Extensive and advanced disease of the pancreas, such as cancer or cirrhosis with lithiasis, gave repeated zero or near zero readings in the duodenal pancreatic enzyme tests. Pancreatic enzyme tests are useful in diagnosing advanced and extensive disease of the pancreas. HARRY W. FINK, MD.

On Subcutaneous Injuries of the Pancreas. V. Taivainen. *Ann. chir. gyn. fenn.*, 1947, 36: 62.

Because of the anatomic location of the pancreas, traumatic injuries of this organ are rare: only about 100 cases were collected from the literature by one author in 1941. In a series of 9,500 autopsies in Finland pancreatic injury was noted twice.

The symptoms of injury to the pancreas are not typical, and depend on the nature of the injury. If there is serious damage involving the blood vessels and pancreatic ducts, immediate pain and increasing signs of peritoneal irritation necessitating prompt operation are present. Generally, blood and pancreatic discharge enter the omental bursa which results in violent symptoms of shock. The foramen of Winslow usually closes, but it may remain open and allow contamination of the general abdominal cavity to occur. Frequently, there is a delay of some 2 hours between the time of the accident and the development of symptoms, and, although a similar symptom-free interval occurs with rupture of other abdominal organs, some workers have considered this symptom-free period to be pathognomonic of pancreatic damage.

A fairly frequent complication of pancreatic rupture is the subsequent development of a pseudocyst; perhaps one-fourth of all pancreatic cysts are of this type. Such pseudocysts usually arise in the lesser omental sac, and are developed in a few weeks or months following the accident. The cyst wall is made up of a thin connective tissue capsule; there are no epithelial elements such as are present in a true pancreatic cyst. The symptoms of a pseudocyst are due to pressure on the adjacent structures such as the stomach (causing nausea and vomiting), the portal vein or vena cava (leading to ascites), or the celiac plexus (causing pain in the upper abdomen and left shoulder).

The diagnosis of pancreatic rupture is exceedingly difficult even with operative intervention because the rupture may involve the posterior surface of the gland and no fat necrosis may be evident. An increase in the serum or urinary lipase and diastase

values may be of considerable value during the first few days even in slight injuries.

Treatment of the injury varies with different surgeons from simple suture of the capsule to tamponade and drainage exteriorly. Pseudocysts are easily broken, and, therefore, are most easily treated by marsupialization, although drainage into an adjacent organ (preferably the duodenum) has been performed.

The author reports a case of pancreatic injury in a previously healthy 11 year old girl who sustained a violent blow to the epigastrium from a bicycle handlebar. Exploratory laparotomy undertaken 3 days later revealed only a yellowish brown peritoneal exudate. Two months later a pseudocyst developed, and following marsupialization an uneventful recovery ensued. WAYNE CAMERON, M.D.

MISCELLANEOUS

"Unexplained" Infarct or Intestinal Apoplexy. Comments on 2 Cases (Infarto "inexplicado" o apoplejia intestinal. Comentario sobre 2 observaciones). **Alfredo Pierini.** *Bol. Acad. argent. cir.*, 1947, 31: 523.

Two distinct types of mesenteric infarcts may be distinguished:

1. The functional type, possibly of an allergic origin, which may subside spontaneously or under the influence of a treatment which combats the shock. This type may lead to vascular thrombosis and a resulting gangrene of the intestines. Adrenaline, on account of its vasopressor effect, has a beneficial effect on the condition.

2. The type caused by mesenteric endarteritis or thromboangitis. Ischemia is attributable to vasoconstriction and therefore an injection of adrenaline is contraindicated. Injection of novocain at the level of the superior mesenteric artery, or spinal anesthesia, in addition to its therapeutic effect, may serve as a test valuable for the differential diagnosis between both types of infarct.

Anaphylactic shock provoked in animals may produce lesions similar to the functional or "unexplained" infarct in man. Allergens responsible for the condition in man may be of alimentary or bacterial origin. The resulting irritation of the sympathetic system in the splanchnic area leads to a functional infarct.

The author reports 2 cases in which a functional type of infarct produced an acute condition of the abdomen. In the first patient, a man 37 years of age, gastrectomy which was performed because of a gastric ulcer with resulting hypochlorhydria, and hepatic insufficiency caused by cholelithiasis, facilitated absorption of some ingested allergen. The operation disclosed a serosanguineous exudate in the peritoneal cavity, cyanosis and dilatation of the small intestines beginning approximately 1 meter below the duodenojejunal junction, and edema of the corresponding portion of the mesentery, with dilated veins and also a dilated superior mesenteric artery. An intravenous injection of 1 mgm. of adrenaline was followed by peristalsis of the intestines (previously immobile) and reappearance of the normal color. The patient made an uneventful recovery.

The second patient, a man 50 years of age, also presented an acute condition of the abdomen. The operation disclosed subperitoneal edema, abundant serosanguineous fluid in the abdominal cavity, purple discoloration of 2 meters length of the small intestines, a hematoma in the corresponding portion of the mesentery, and a dilated superior mesenteric artery. Intramuscular injections of 1 mgm. of adrenaline were followed by persistalsis and normal color of the intestines. The patient recovered from the operation. JOSEPH K. NARAT, M.D.

The Effect of Radiation Therapy on the Nocturnal Gastric Secretion in Patients with Duodenal Ulcer. A correction. **Erwin Levin, Anna Hamann, and Walter Lincoln Palmer.** *Gastroenterology*, 1947, 8: 565.

The third paragraph of this abstract which appeared on page 554 of the December, 1947 issue reading: "Treatment consisted of the daily application of 1,350 to 1,710 roentgens to the body and fundus of the stomach through two portals located anteriorly and posteriorly, and was carried out for a period of 10 to 14 days" is not correct. The authors' own words are as follows: "All patients received a depth dose of 1,350 to 1,710 to the stomach in daily treatments through a period of 10 to 14 days. This was obtained by giving individual doses of 300 as measured on the skin with backscatter, through two portals measuring 13 by 13 centimeters located over the body and fundus of the stomach, anteriorly and posteriorly."

GYNECOLOGY

UTERUS

Is Extensive Mutilating Surgery of Cancer of the Uterus Justified in the Light of Modern Knowledge? (Alla luce delle moderne conoscenze, nella terapia del cancro dell'utero, hanno ancora ragione di sussistere le tecniche chirurgiche ampiamente demolitrici?). **Aldo Gusso.** *Riv. ostet. gin.*, 1947, 2: 107.

Of 213 epitheliomas of the uterus, 33 (15 per cent) were located in the corpus and 180 (85 per cent) in the cervix. Of the 33 cases of cancer of the corpus, 7 (30 per cent) were operable, and of the 180 cases of cancer of the cervix, 30 (12 per cent) were operable.

Invasion of the lymphatics occurs only as an exception during the first 2 or 3 months of the existence of a malignant lesion.

Cancer of the cervix invades first the so-called interureterouterine triangle. The author maintains that surgical intervention is useless and illogical if the cancer has invaded tissues beyond this triangle.

Radium introduced into the vagina and uterus is not capable of producing a cure, as a rule, but may be advantageously employed prior to the operation. Roentgen therapy and so-called plesioroentgen therapy or contact irradiation according to Chaoul's method also fails to produce a radical cure. Best results may be expected from applications of radium to the vagina and uterus followed by a hysterectomy and supplemented by deep x-ray therapy.

The terms "radium surgery" and "roentgen surgery" are applied to a concurrent use of surgery and irradiation. Theoretical considerations induced the author to prefer radium surgery to roentgen surgery although the method is not harmless.

The author came to the conclusion that cancer of the uterus is a curable disease and that the chances of cure are in direct proportion to the earliness of treatment. JOSEPH K. NARAT, M.D.

A Discussion of the Preference for Total Abdominal Hysterectomy instead of Subtotal Hysterectomy (Sulla discussa preferenza da darsi all'isterectomia totale addominale in confronto all' isterectomia subtotale). **E. Debiasi.** *Fol. gyn.*, Genova, 1947, 42: 223.

A comparison is made between total abdominal hysterectomy, and subtotal hysterectomy with regard to the morbidity, mortality, and complications of both. In the authors personal series of 181 hysterectomies for benign lesions, he had a mortality rate of 1.1 per cent.

Factors in favor of total hysterectomy are as follows: (1) it is a radical procedure; (2) the mortality rate is relatively low; (3) the danger of cancer is eliminated; (4) morbid changes in the stump are eliminated; (5) there is relative infrequency of postoperative pelvic infiltrations; (6) there is a low frequency of postoperative disturbance of the intestinal function, such as meteorism, and (7) it has a minor effect on the pulse.

Factors in favor of subtotal hysterectomy are that (1) it requires less time; (2) the mortality is less than that of total abdominal hysterectomy; (3) the normal shape of the vaginal wall is maintained; (4) the technique is easier, especially when the pelvic floor is rigid; (5) there is slightly less postoperative disturbance of the digestive tract; and (6) there is less frequency of wound separation.

Both procedures are favorable with regard to temperature, respiratory disturbances, period of bed confinement, the possibility of preservation of the adjoining organs, and the possibility of secondary intervention.

The author advocates complete hysterectomy as a standard procedure and believes that the subtotal procedure is indicated only in the presence of special considerations, such as a desire to maintain the menstrual flow, technical difficulties, and the necessity to shorten the procedure in view of a grave condition of the patient. ARTHUR F. CIPOLLA, M.D.

ADNEXAL AND PERIUTERINE CONDITIONS

A Classification of Ovarian Tumors Based upon Histogenesis. John A. Spencer and Philip J. Reel. *Am. J. Obst.*, 1947, 54: 273.

The study of ovarian tumors has received a tremendous impetus of late years because of the careful study, investigation, and reporting of a goodly number of the more unusual neoplasms, and the attempt to work out a truly scientific classification on a histogenetic basis. The anatomicopathologic type of classification has been utilized by most pathologists to date. Histogenesis should shed additional light on these tumors when they are viewed from the broader clinical standpoint, particularly in regard to treatment and prognosis. From the radiologic viewpoint, a more universal classification based on a histogenetic background would clear up the present very confused literature on the effect of deep therapy.

It is still necessary to use descriptive terms to name different neoplasms properly, but it is no longer practical merely to classify these growths into the cystic and solid and benign and malignant. In the absence of a universally accepted histogenetic classification, the authors present a modification of the one suggested by Schiller.

Ovarian neoplasms are divided into three broad classes:

1. Ovariogenetic tumors: derived from ovarian tissue.
2. Nonovariogenetic tumors: derived from tissues foreign to the ovary but found elsewhere
3. Carcinomas of undeterminable histogenesis.

Following this basic structure and filling in the subdivisions led to the following classification:

1. Ovariogenetic (tumors developing from tissues of true ovarian structure)
   A. From the mesenchymal core of the ovary.
      (1) From fetal cell remnants without error in sex chromosomes
         (a) Granulosa cell tumor
         (b) Theca cell tumor
      (2) From fetal cell remnants with error in sex chromosomes
         (a) Arrhenoblastoma—male
         (b) Disgerminoma—neuter
      (3) From interstitial tissues without sex potential
         (a) Fibroma
         (b) Angioma
         (c) Myoma and fibromyoma
   B. From the surface epithelium of the ovary (prosoplasia toward the muellerian duct)
      (1) Serous cystoma (tube)
      (2) Endometrioma (endometrium)
      (3) Pseudomucinous cystoma (cervix)
2. Nonovariogenetic (tumors developing from tissues not normally present in the ovary)
   A. By displacement into the ovary in fetal life
      (1) Early—teratoma
         (a). Mature—dermoid
         (b). Immature—embryoma
      (2) Late—tissue from structures contiguous to the ovary during embryological development
         (a) Hypernephroma—adrenal
         (b) Mesonephroma—kidney
         (c) Brenner tumor—urogenital epithelium
         (d) Ganglioneuroma—sympathetic ganglia
   B. By displacement into the ovary in adult life
      (1) Metastases of malignant tumors—Krukenberg.
3. Carcinoma of undeterminable histogenesis
   A. Carcinoma simplex, scirrhous carcinoma, plexiform carcinoma

A discussion of the histogenesis of each tumor is presented. The value of this concept lies in its aid toward the diagnosis, treatment, and prognosis of ovarian tumors. JOHN R. WOLFF, M.D.

EXTERNAL GENITALIA

Microbial Pictures in Vaginal Smears. New Classification of Vaginal Biocenosis into 6 Basic Types. (Mikrobní obrazy poševní. Nové třídění poševní biocenosy na šest základních obrazů). **O. Jírovec, R. Peter, and I. Málek.** *Čes. gyn.*, 1947, 12: 1.

Mere bacteriological classification of the cleanliness of the vagina into grades does not satisfy clinical needs, for it omits the gonococci, protozoa (Trichomonas vaginalis), and phytozoa (mycoparasites, yeast micro-organisms).

With regard to the entire microfauna, microflora, and the histological elements, the authors classify the vaginal biocenosis from the broader microbiological point into 6 basic groups, which they call microbic vaginal smears, and they number them with Roman figures (I-VI).

The basic microbic vaginal smears and their types are:

I. The normal physiological smear from the vagina of a healthy adult woman. Types a, b, and c: epithelial cells, few leukocytes (according to the phase of the menstrual cycle). Doederlein bacilli. Type d: transition type. There is an increase in the number of leukocytes and bacilli.

II. Nonpurulent bacterial discharges (Type a): epithelial cells, few leukocytes and Doederlein bacilli, varied flora of bacilli and cocci. Type b: Vibrio type. Type c: transition type, semipurulent: more leukocytes.

III. Purulent bacterial discharges. Type a: few epithelial cells, many leukocytes, varied flora of bacilli and cocci. Type b: Streptococcal type. Type c: Spirochaeta and fusiform bacteria type or both. Type d: leptothrix type.

IV. Gonorrheal discharge. Type a: acute. Type b: chronic.

V. Trichomonas discharge. Type a: fresh infection: many leukocytes, scanty Doederlein bacilli, more or less trichomonads. Type b: culminating infection: abundant trichomonads and leukocytes, varied flora of bacilli and cocci. Type c: chronic or latent infection (few trichomonads, few leukocytes, otherwise similar to type IIa.)

VI. Vaginal mycosis. (Type a): nonpurulent mycosis: few leukocytes, bacilli Doederlein, few epithelial cells and some kinds of pseudomycelium and conidium. Type b: purulent mycosis: many leukocytes, the rest like type a.

For the clinician it is quite sufficient to remember the basic groups (I-VI), because the microbiologist informs him in slogans, e. g., microbic smear II, vibrio; or microbic smear V, fresh infection. The authors' experiences showed that nowadays we cannot do without a classification of the vaginal biocenosis from the broader microbiological viewpoint and that the treatment should be scientifically causal.

MISCELLANEOUS

Menstrual Toxin. Experimental Studies. O. Watkins Smith. *Am. J. Obst.*, 1947, 54: 201.

The atypical euglobulin derived from the endometrium during its late stages of retrogression is experimentally a powerful tissue damaging agent, capable also of inducing endocrine changes indicative of increased secretion and release of gonadotropic as well as of adrenotropic hormones. Immunologic studies suggest that this menstrual toxin and Menkin's canine necrosin are probably identical, which brings into close relationship the tissue damage in 2 species from different causes.

Fibrinolytic activity has been demonstrated to be closely associated with menstrual toxin and canine necrosin, and fibrinolysin has been found in the circulating blood during menstruation, labor, and the

toxemia of pregnancy, also following surgery and in human pleural and peritoneal exudates.

The pseudoglobulin fractions of all these fibrinolysin containing fluids, with the exception of the circulating blood following surgery, have the property of prolonging the survival time, and even occasionally of saving the lives, of immature rats given minimal lethal doses of menstrual toxin. This property requires painstaking, controlled experiments for its demonstration. Concentration of the pseudoglobulins is necessary. Protection appears to be a matter of quantitatively neutralizing the toxin and not of antibody formation in the ordinary immunologic sense. JOHN R. WOLFF, M.D.

Actinomycosis of the Internal Female Genitalia. Report of 2 Cases. Everett M. Baker. *West. J. Surg.*, 1947, 55: 501.

Actinomycosis may involve almost any organ of the body, but comparatively few cases of this condition have been reported. A comprehensive review of the literature on this disease of the ovary and internal female genitalia has recently been made by the author.

Actinomycosis of the ovary is a relatively rare disease. It is an infectious granulomatous disease characterized by the destruction of tissue, suppuration, and an overgrowth of fibrous tissue. Most of the reported cases have been in the right ovary.

The diagnosis is not easy even during laparotomy. The pockets of pus containing the ray fungus may not be clearly evident. The pathology resembles that of a neoplasm, but being essentially inflammatory, search for the elements of inflammation is imperative. Microscopic examination often fails to bring out the fungus immediately. The organism is slow in its invasion and slow in producing symptoms. A previous history of appendicitis or of a pelvic operation with an unusually slow and stormy recovery should make one suspicious of pelvic actinomycosis.

Many types of treatment have been offered but the most important factor is early diagnosis.

Two cases of pelvic actinomycosis are reported in detail. HARRY W. FINK, M.D.

Hemorrhages in the Menopause; the Clinical Significance of an Endometrium with Signs of Hormonal Influence (Ueber Blutungen in der Menopause. Speziell der klinischen Bedeutung eines Endometriums mit Zeichen hormonaler Beeinflussung). *Acta obst. gyn. scand.*, 1947, 27: Supp. 6

The pathogenesis of postmenopausal vaginal hemorrhage, particularly in patients in whom the endometrium shows signs of response to hormonal stimulation, is discussed. Only patients who have been in the menopause for at least a year are considered. The necessity of excluding the presence of a malignant tumor in these cases is emphasized.

The problems involved in the classification of different types of endometrial hyperplasia and their microscopic appearance having been discussed, attention is called to the importance of differentiating the curettings from the endometrium which shows signs of response to hormonal stimulation, from those taken in the presence of "retrogressive hyperplasia" or a uterine polyp. The latter have not been given sufficient prominence in the literature concerning endometrial hyperplasia in the menopause. The differentiation is difficult but may be materially facilitated by co-operation between the gynecologist and the pathologist and by constant examination of the uterine cavity with a uterine canal forceps. Attention is drawn to the microscopic details, which, in the experience of the Radiumhemmet, make the diagnosis of a uterine polyp from curettings possible.

The literature concerning the etiology of an endometrial hyperplasia in the menopause is carefully studied, particularly with regard to the coincidence between this condition and ovarian tumors of different types. A thorough description is given of the estrogen findings in the urine from patients with granulosa cell and theca cell tumors.

One hundred and forty-eight cases of postmenopausal bleeding are presented in which the uterine mucosa showed signs of response to hormonal stimulation. The classification of the patients is made with reference to the following data noted at the first examination:

1. Those with an ovarian tumor (30).

2. Those with a history of previous treatment with estrogenic hormones for a fairly long period or in considerably large doses (31).

3. Those without an ovarian tumor and without a history of previous treatment with estrogenic hormones (87). These are classified with reference to the history of their last menstrual period: less than 2 years previous to the postmenopausal bleeding (28), and more than 2 years (59). The reason for this grouping is that the cessations of the uterine and the ovarian cycles do not correlate with the menopause and that, consequently, bleedings of climacteric type may occur during the first years after the menopause.

Thirty-six patients were in the menopause less than 2 years and received no treatment with estrogenic hormones. In 8 of these an ovarian tumor was present at the first examination. Only in 2 of the remaining 28 patients was an ovarian tumor noted later. The different microscopic appearance of the endometrium is briefly discussed.

A close study is made of 81 patients who were in the menopause for more than 2 years and had received no treatment with estrogenic hormones. In 22 of these an ovarian tumor was present at the first examination. Of the 81 patients, 70 were of great interest with regard to the pathogenesis of the endometrium, which showed signs of response to hormonal stimulation in the menopause. The remaining 11 patients are not further discussed because:

1. It was impossible to decide if disintegrated pieces of an endometrial hyperplasia or only of an endometrial polyp were present in the curettings (8).

2. No biopsy of the uterine mucosa was made (2).

3. It was impossible to decide the nature of the amenorrhea (1). The patient had been treated for several years with roentgen rays and the possibility of a temporary sterilization could not be excluded.

The microscopic appearance of the uterine mucosa in the 70 cases mentioned is discussed and a detailed account of the clinical course is given. In view of the clinical course and of the sex hormone findings in the urine, it is most probable that ovarian tumors were present in at least 65 of the 70 patients (92.9%). In 53 of these 70 patients a laparotomy was performed. Microscopic verification of the ovarian tumors was available in 49 lesions: 42 granulosa cell or theca cell tumors (85.7%), 1 luteinoma (2%), 3 pseudomucinous papillary cystadenomas (6.1%), and 3 malignant papillary cystadenomas or adenocarcinomas of the ovary (6.1%). Three of the 49 ovarian tumors were histologically malignant and 5 were clinically malignant; 11.9 per cent of the granulosa cell tumors were clinically malignant.

The Radiumhemmet series of postmenopausal bleedings includes 90 cases in which clinical and histological examinations revealed nothing but a uterine polyp. Two of the patients were previously operated upon for carcinoma of the stomach, and later developed metastases in both ovaries. A third patient has not been traced. Two of the remaining 87 patients later developed an ovarian tumor (2.2%). The considerable difference between the appearance of an ovarian tumor in patients with nothing but polyps (2.2%), and that of such a tumor in patients with endometrial hyperplasia (92.9%) obviously demonstrates the importance of a proper microscopic interpretation of the curettings.

In 8 of the 51 granulosa cell and theca cell tumors included among the 148 patients, there was a coincident adenocarcinoma of the fundus uteri (15.7%); 2 of these were histologically verified and 6 were considered as Group IX in the classification of Reuterwall.

Three of the 8 patients were subjected to repeated curettage and it was noticed that the epithelial cells became increasingly atypical. The experience at the Radiumhemmet differs from that of Novak and Taylor who believe that the proliferative forces responsible for benign hyperplasia may predispose to the development of cancer.

In agreement with what has been stated before, it is advisable to submit to laparotomy all patients whose uterine mucosa shows evident signs of response to hormonal stimulation after being in the menopause for 2 years, and who have received no treatment with estrogenic hormones. In cases in which it is impossible to perform a laparotomy, radiological treatment is indicated. Granulosa cell tumors may be very radiosensitive.

The patients in whom it is impossible to differentiate between an endometrium with signs of response to hormonal stimulation and disintegrated pieces of an endometrial polyp should be kept under observation.

The connection between the type of the supplied estrogenic hormone and the microscopic appearance of the uterine mucosa is discussed.

Analysis is made of the estrogenic hormones in the urine from patients in the menopause. An increased amount signifies the presence of a granulosa or theca cell tumor.

OBSTETRICS

PREGNANCY AND ITS COMPLICATIONS

Clinical-Statistical Study of Cases of Hyperemesis and Eclampsia Observed in the Clinic of Siena during the Period from 1929 to 1943 (Considerazioni clinico-statistiche sui casi di iperemisi e di eclampsia osservati nella Clinica di Siena nel quindicennio 1929-1943). *Arch. ostet. gin.*, 1946, 51: 173.

Three theories of the pathogenesis of hyperemesis and eclampsia may be distinguished: (1) the placental, (2) the endocrine, and (3) the theory based on alterations of the autonomic nervous system. Innumerable intermediate theories have also been advanced.

During the period from 1929 to 1943, 25 cases of hyperemesis and 70 cases of eclampsia were observed in the Clinic of Siena. Hyperemesis was recorded in 0.3 per cent and eclampsia in 0.9 per cent of the entire obstetrical material. Of the 70 cases of eclampsia, 8 occurred during pregnancy, 5 toward the end of pregnancy, 38 during the labor, and 19 in the puerperium. The predominance of cases during labor may be attributed to the untoward effect on the liver and kidneys of the effort of the organism to expel the fetus.

Recovery was recorded in 47 cases, or 67.1 per cent. Twenty-seven patients who recovered had the eclampsia in labor, 11 in the puerperium, 5 during pregnancy, and 4 at termination of the pregnancy. The percentage of the recoveries was higher in the women younger than 35 years than in older ones.

Fatalities occurred in 17 cases: in 6 of the patients who had eclampsia in the puerperium; in 8 who had it during labor; in 2 having it during pregnancy; and in 1 patient who had it at the end of the pregnancy.

Operative procedures were employed in 46 patients, forceps accounting for 52.1 per cent of the operations, and version and extraction, cesarean section, and induction of abortion accounting for the rest. Of 24 patients in whom forceps were applied, 4 died. Of 12 patients who were subjected to version, 5 died and of 6 who underwent cesarean section, 1 expired.

Seventeen fetuses, or 33.3 per cent, died.

The author favors the placental theory of eclampsia, which attributes the condition to autointoxication with poisonous substances originating from the fetus.

Hyperemesis is treated by the author symptomatically with sedatives, hormonal preparations, opiates, and products causing hyperglycemia. Individualization is required because one drug may be efficient in one patient but not in another.

Eclampsia in the early stages is treated with venesection, intravenous injection of magnesium sulfate, the administration of sodium sulfate by enema, and the use of decholin or other cholagogues, or sedatives. In pronounced eclampsia in multiparas the author recommends termination of the pregnancy through the vaginal route by podalic version, the application of forceps, or craniotomy. In primiparas the author advocates cesarean section.

ARTHUR F. CIPOLLA, M.D.

Tuberculosis and Pregnancy. I. Bluhm. *Acta med. scand.*, 1947, 128: Supp. 197.

In the beginning of the twentieth century pregnancy was generally considered to have a deleterious influence on tuberculous women. By and by, investigators altered the opinion as to this problem. Even nowadays, however, the majority of authors are of the opinion that pregnancy might influence tuberculosis, while the minority consider the tuberculous process to be independent of pregnancy. It has been pointed out that progression may occur post partum, especially in cases with cavities. This is attributed to the descent of the diaphragm after delivery, and the forced ventilation in connection with labor itself. Further, it is stated that progression might be prevented by collapse treatment, e.g., pneumothorax or thoracoplasty. Pneumothorax might well be established during pregnancy.

The author has collected material in the Central Dispensary of Stockholm. Parturition occurred in the year 1945, and the patients were controlled before pregnancy, throughout gestation, and after delivery.

The material comprises 121 patients, 115 of whom were not subjected to surgical treatment. There are 5 with pneumothorax, and 1 patient with thoracoplasty. In the 115 cases first mentioned, the tuberculous process was stationary in 83 per cent during pregnancy and the control period afterward. Progression was seen in 7 per cent and regression in 5 per cent. In 5 per cent both progression and regression were found.

As regards the cases with progression, the tuberculous changes were benign. The fact that they most frequently occurred immediately post partum indicates that the physical effort of the labor itself might play a certain role. Otherwise there were no signs to be found among these patients that suggested that the pregnancy had any influence upon the tuberculous process. In the cases with regression, improvement may begin before or after the patient has become pregnant as well as before or after delivery. The number of cases with mere regression (5%) corresponds fairly well to that of those with mere progression (7%). Thus, it is evident that the alterations which occur now and then during pregnancy might well be ascribed to the usual clinical changes in tuberculosis.

In the 5 per cent in which progression alternated with regression during pregnancy there was no correspondence in the course of the changes. In these cases there was no marked deterioration post partum.

Among those cases in which the tuberculous process was stationary throughout gestation, there were a great number of patients who, as regards the activity and the extension of the pulmonary disease, were quite comparable to those with progression. Hence, it is evident that it is impossible to prognosticate the course of the disease during pregnancy. The thesis, maintained by many authors, that the tuberculous process must be stationary before pregnancy, is not supported by these investigations.

In the 5 cases with pneumothorax and the only case with thoracoplasty no changes were found in connection with pregnancy.

Thus, since the investigations show that pregnancy would hardly influence the course of the tuberculous disease, the author, in full agreement with several other authors of recent years, has arrived at the conclusion that abortion should hardly ever be carried out. It is of great importance, however, that the patients be carefully controlled, eventually have sanatorium care, and, if necessary, be subjected to collapse treatment. Abortion is not indicated, even in cases of active pulmonary tuberculosis.

CHARLES BARON, M.D.

Roentgen Diagnosis of Intrauterine Death of the Fetus (Diagnóstico radiológico da morte intrauterina do feto). **João Amorim, Eduardo Cotrim, Oswaldo Lacreta, and Antonio Clemente Filho.** *An. brasil. gin.*, 1947, 12: 437.

The authors review the clinical signs and symptoms of intrauterine death of the fetus and emphasize the importance and significance of the roentgen signs which, according to Thomas (1940), include deformity of the skull, hyperflexion of the spine, overriding of the cranial bones. asymmetry of the skull, separation of the cranial bones, lack of proportion between the size of the fetal bones and the age of the pregnancy, and loss of sharpness of contour of the fetal bones.

As the roentgen signs of death of the fetus result from changes in the soft tissues, they will become visible only when these changes reach a certain degree. The paralysis of the muscles and their maceration and disintegration allow the dead fetus to assume attitudes which it could hardly assume if it were living.

Deformity of the skull and overriding of the cranial bones (Spalding's sign) were constant findings in the authors' roentgenograms of dead fetuses. Hyperflexion of the spine appeared less frequently than Spalding's sign. In 1 of their cases there was wide separation of the cranial bones, which gave the impression that 2 skulls were present. After delivery of the macerated fetus, it was found to be hydrocephalic. The reabsorption of the cerebrospinal fluid had produced collapse of the parietal bones, which produced an image that is probably characteristic of intrauterine death of a hydrocephalic fetus. The authors have not encountered any description of such an image in any of the works which they have consulted.

The order of appearance of the various signs is not always the same. In addition, it is out of the question to take into consideration only 1 sign; all of the signs as a whole must be evaluated. It is possible that the sign described by Boyd Roberts (the presence of gas in the circulatory system of the fetus which has been dead for more than 60 hours) may represent a valuable one for the early roentgen diagnosis of intrauterine death of the fetus.

RICHARD KEMEL, M.D.

LABOR AND ITS COMPLICATIONS

The Prognosis and Therapy of Parturition in Women with Contracted Pelvis and Breech Presentation (Prognosi e terapie del parto in presentazione podalica nei bacini limite). **Pier Luigi Bianchi.** *Ginecologia, tor.*, 1946, 12: 307.

Moderately contracted pelvis is not infrequently overlooked by nonspecialists. Fortunately, the condition is not serious unless combined with an abnormal presentation.

Frontal and face presentations, especially in primiparas, combined with a contracted pelvis do not merit any special attention because of their rarity.

Roentgenography is of great value for an early diagnosis of contracted pelvis complicated by an abnormal presentation.

Of 611 cases of breech presentation, 51 (8.3 per cent) were found in women with a contracted pelvis. Seventy-two newborn infants (11.7 per cent) died. Twenty (39.2 per cent) of the women with a contracted pelvis and breech presentation lost their fetus. The ratio of multiparas to nulliparas (with a contracted pelvis and breech presentation) was 1 to 1.3. Twenty-five per cent of the multiparas and 50 per cent of the primiparas lost their fetus.

Complete podalic presentation in which the breech and feet simultaneously reach the pelvic cavity was found in 69 or 11.3 per cent of the 611 women with podalic presentation, while in 542 patients the presentation was incomplete.

The incomplete presentation may be subdivided into two groups: buttock presentation and the type with procidentia. In the first group the mortality of the fetuses was 44 per cent and in the second, 33 per cent.

The author concludes from his observations that a combination of contracted pelvis and podalic presentation requires surgical intervention. Presentation with procidentia gives a better fetal prognosis than the buttock presentation. The fetal prognosis is particularly grave in primiparas. In primiparas low cesarean section is indicated unless there are contraindications, such as infection of the uterine cavity or insufficient vitality of the fetus. In multiparas whose previous deliveries did not terminate spontaneously, there is no reason, it is believed, why a vaginal intervention in the form of a prophylactic lowering of one of the feet should not be employed.

ARTHUR F. CIPOLLA, M.D.

Lymphopathia Venereum Complicating Labor. Irwin H. Kaiser and Edwin L. King. *Am. J. Obst.*, 1947, 54: 219.

Lymphopathia venereum complicates pregnancy primarily by the inflammatory lesions it produces in the mother, which impede the progress of labor. The dystocia produced by this disease falls into 2 anatomic groups. The first is caused by the elephantiasis esthiomene variety of vulvar lesions. Its management in nowise differs from that of similar soft tissue outlet dystocia due to other causes. The second type is caused by the extensive scarring of the soft tissues in the pelvis, of which the rectum is usually the first involved. This is due primarily to the virus and also to the usually associated secondary infection. The problems presented by this second type are unique in obstetrics.

This report is based on an analysis of 38 labors in 28 women with pelvic lymphopathia venereum observed at the Charity Hospital in New Orleans, Louisiana, between 1937 and 1946, plus a survey of 124 instances of this condition which appeared in the literature.

No individual is known to have had an exacerbation of the lymphopathia in association with pregnancy.

The 162 labors now recorded in the literature have a maternal mortality rate of 6 per cent, but this figure appears to exaggerate the actual risk. Force in delivery has played a large role in the reported fatalities. Version and extraction is absolutely contraindicated. Death is usually due to rupture of the rectum or uterus, which may occur with spontaneous delivery.

If soft tissue scarring due to lymphopathia venereum is widespread in the pelvis, the patient should be delivered by cesarean section. A trial of labor may be permitted but if the presenting part fails to descend to the outlet, cesarean section rather than any form of pelvic delivery should be performed, regardless of the dilatation of the cervix. If the patient delivers per vaginam, she should be watched diligently for signs and symptoms of rupture of the uterus or rectum. The appearance of peritoneal irritation or shock should suggest exploratory laparotomy.

Colostomy in itself presents no special obstetric problem other than that found in other patients with pelvic lymphopathia venereum. In the 38 labors in the presence of lymphopathia venereum and rectal stricture observed in the Charity Hospital in New Orleans, there were no maternal deaths. Three cesarean sections were performed.

JOHN R. WOLFF, M.D.

Painless Labor with Continuous Caudal Analgesia (O parto indolor pela analgesia caudal continua). Francisco Cerrutl and Menotti Laudisio. *Rev. Paulista med.*, 1946, 29: 1.

Using a steel needle, in preference to a catheter, and 1 per cent novocain in physiologic salt solution at the rate of 30 drops per minute for the first 20 minutes and 15 drops per minute subsequently, the authors tried the method of continuous caudal analgesia in 20 cases of labor and succeeded in introducing the anesthetic in 17. They found it impossible to pass the needle through the sacrococcygeal hiatus in 2 cases, and the needle perforated a vein of the epidural space in 1 case, causing inundation of the sacral canal. Analgesia was complete in 13 cases and partial in 4. There were no accidents or complications and no fetal deaths. The largest quantity of anesthetic used was 350 c.c. and the smallest 50 c.c. The maximal duration of anesthesia was 6 hours and 25 minutes, the minimum 50 minutes. The authors draw the following conclusions.

Under continuous caudal analgesia a painless labor can be obtained in from 70 to 80 per cent of the cases. The anesthetic should be started when labor is in full swing, with a cervical dilatation of not less than 3 to 4 cm., and the method should be used only in cases in which transpelvic delivery is possible.

Continuous caudal analgesia usually causes a decrease in the frequency of the uterine contractions with slight shortening of their length and, according to the level of the cutaneous anesthesia, may produce secondary inertia. Nevertheless, delivery is not prolonged because anesthesia facilitates cervical dilatation and allows the fetal head to reach the pelvic floor more quickly.

The fetal head frequently stops at the perineum because the abdominal wall is anesthetized and the patient is unable to exert voluntary action. Kristeller's maneuver of expression eliminates this deficiency and becomes almost indispensable to delivery of the cephalic pole. However, an abdominal belt was used in 2 cases and found to replace Kristeller's maneuver to advantage because it exerted more uniform pressure. When these artifices do not result in spontaneous delivery, a low forceps may be applied. In occiput right posterior presentation the fetal head frequently reaches the perineum without the occurrence of internal rotation.

One of the greatest difficulties encountered in continuous caudal analgesia is the introduction of the needle into the sacral canal because edema of the region often covers up the sacrococcygeal triangle which is an indispensable reference point for the correct placing of the needle.

Uninterrupted observation of the patient is essential during the use of the method. In their cases the authors encountered a sudden rise of the cutaneous level of anesthesia, complete and rapid anesthesia with small quantities of anesthetic, a fall in the blood pressure, and other occurrences which required the immediate intervention of the anesthetist.

The drip method is superior to the fractionated dose method because it is easy to change the number of drops used when this becomes necessary, while 20 or 30 c.c. of anesthetic solution injected at one time cannot be withdrawn from the sacral canal. The method also allows the use of 2 tests: one to detect perforation of the dura mater, the other to identify a wrongly placed needle.

The arterial pressure must be taken frequently because in some patients low pressure is the earliest sign of too high a level of anesthesia. The best level for the anesthesia in order to obtain painless uterine contractions without effect on the maternal and fetal organisms is that of the umbilicus. As this level is passed there is a gradual fall in the arterial pressure, which may exceed 30 mm. of mercury.

Continuous caudal analgesia always decreases the blood loss accompanying detachment of the placenta. It allows manual dilatation of the cervix and the application of forceps without pain. It produces complete cervical, vaginal, and perineal relaxation and frequently solves serious cases of dystocia from excessive contractions, especially in Schickele's syndrome. It is also the best method for the delivery of premature infants because it eliminates spasm and decreases the traumatic effect of normal labor on the infant's weak skull. Finally, it has no evident harmful effect on fetal vitality as fetal anoxia due to a great fall in the maternal blood pressure can be prevented by oxygen therapy.

The medical press should present the real value of the method and stress that it is dangerous when used by the inexperienced physician.

RICHARD KEMEL, M.D.

NEWBORN

A Study of the Causes of Fetal and Neonatal Mortality on the Obstetric Service of Bellevue Hospital. John S. Labate. *Am. J. Obst.*, 1947, 54: 188.

While a definite reduction in the maternal mortality rate of the United States has been recorded in the past decade, the reduction in the fetal and neonatal mortality has not been proportionate. In order to effect an adequate reduction in this rate, it is important to obtain accurate information concerning the causes of death in stillbirths and in newborn infants. This object can best be obtained through careful autopsy examinations, correlated with the clinical facts related to this fatality. The author attempts to analyze the causes of such deaths on the obstetric service of Bellevue Hospital, New York.

The four major causes of fetal and neonatal deaths, as determined from this study, were found to be prematurity, pulmonary lesions, birth trauma, and maceration following antepartum or intrapartum fetal deaths.

Prematurity was found to be the greatest single cause of death. In 27.6 per cent of all the autopsies, it was believed that death occurred because the vital organs were insufficiently developed to carry on with the proper functioning necessary to maintain life. At postmortem examination, the only findings were those attributable to immature development of the vital organs of the body. From these observations, obstetricians might be tempted to absolve themselves of all responsibility in handling premature infants, and to throw the burden entirely upon the shoulders of the pediatrician; however, the obstetrician plays a vital role in the initial handling of these cases. He must attempt to delay the onset of labor as long as possible, avoid excessive use of sedation during labor, and shorten the second stage of labor by early episiotomy and low forceps delivery. Immediately after delivery, energetic measures must be taken to initiate respirations, maintain body temperature, prevent cyanotic attacks, encourage proper nutrition, and prevent infection.

Pulmonary lesions accounted for 22.5 per cent of deaths. Aspiration of amniotic fluid produced 60 per cent of this pulmonary pathology. Pneumonia was the second most frequent type of lung lesion encountered at autopsy. Hemorrhage and the presence of a hyaline membrane caused pulmonary lesions also.

Birth trauma accounted for 16.9 per cent of the deaths. These injuries fell into three main groups—intracranial, spinal, and intra-abdominal.

A large group of babies, 16.5 per cent, were in a state of extensive maceration. Detailed anatomic dissection or microscopic study was impossible. In over half the cases of maceration, no maternal cause for death of the fetus could be determined. In the remainder, however, some maternal abnormality was present. Toxemia, premature separation of the placenta, prolapse of the cord, obstruction of the umbilical cord by knots, and systemic infection caused fetal deaths.

Prematurity alone is the greatest cause of fetal and neonatal mortality. It appears obvious that any marked reduction in the gross neonatal mortality must be brought about by a reduction in premature births, or by reducing the number of deaths from prematurity. The lessons learned at the autopsy table should be carried to the delivery room and the nursery. An understanding of these causes of fetal deaths will lead to preventive measures. The death rates from prematurity, pulmonary lesions, and birth trauma, which constitute the three major causes of death, can be greatly reduced. Similarly, fetal death from syphilis, infection, and erythroblastosis is preventable to a considerable degree.

JOHN R. WOLFF, M.D.

MISCELLANEOUS

Studies in Changes in the Placenta, with Particular Reference to Possible Injuries to Villi and the Fetal Vessels. John Næslund and Per Arén. *Acta obst. gyn. scand.*, 1947, 27: 115.

The normally impermeable wall of the placenta sometimes allows substances to leak out from the fetal to the maternal blood stream, and vice versa. This has been proved by experiments employing radioactively tagged blood cells, and by certain American investigators using different animals and radioactive sodium. The latter found that in animals the passage of sodium through the placenta increases materially with the progress of pregnancy, and that there is a definite correlation between the changes in the structure of the placenta and the

variations in the rate of transfer of substances during different periods of pregnancy.

In women also, the results of investigation following the intravenous injection of radioactive sodium showed that the rate of transfer of sodium per unit of weight of the placenta rose noticeably with the progress of pregnancy. The authors correlate certain morphological findings observed by them with this conclusion. They found that in the early stages of pregnancy, the villi were relatively few but, at the same time, large and thick walled, and covered both by Langhans and by syncytial layers; in later stages the villi increased in number and at the same time became smaller and more thinly walled, and without a Langhans layer.

By means of serial section examination of the placental tissue, the authors endeavored to demonstrate the changes of villi or their vessels which might explain a raised permeability in the placental wall under certain conditions; placentas were selected which showed marked structural changes grossly, such as are often found in toxemic patients.

One such placenta from a woman with toxemia is described. The patient had been given a transfusion of blood containing elliptocytes before delivery, and a number of the cells were seen to have gone over to the fetus. Several variously sized, dark, blood-filled foci stood out plainly in a microsection of the fixed placenta. The villi were considerably wider apart than in the normal placental tissue and their vessels were engorged with blood. Serial sections of a villus wall showed it growing thinner and thinner, with the capillaries finally seen lying naked in the intervillous spaces; at places the walls were indistinguishable between tightly packed fetal red cells which seemed to pass directly into the intervillous spaces of the mother. In places only a thin endothelial layer separated the fetal and maternal blood. Some sections demonstrated villi with walls without the syncytial layer. Gaps in the villus walls were seen filled with compact blood cells, both fetal and maternal.

Injection experiments on placentas with sterile solutions of rice starch of a certain size of grain were carried out. The umbilical vein of a fetus delivered by cesarean section (in the case of an induced abortion for medical reasons) was injected with the starch solution, the fetus being allowed to live while the blood was pumped around the body and into the placenta. Histological examination of the placenta revealed rice grains in the villus vessels, although none were seen in the villous spaces. Villus wall changes favoring the passage of substances from fetus to mother were noted. PHILIP B. CHASE, M.D.

The Results of Three 5 Year Studies of Hydatid Mole and Chorioepithelioma on the Pacific Coast. Albert W. Holman and Elizabeth H. Schirmer. *West. J. Surg.*, 1947, 55: 525.

This article is based on a combined 15 year study and includes the findings reported on 426 moles and 107 cases of chorioepitheliomas; 69 of the latter followed hydatid mole.

Hydatid mole in this series was not as common in patients over 40 years of age as it was thought to be by other observers. Hydatid mole is a disease of the ovum in early pregnancy. The teaching that excessive enlargement of the uterus occurs in the majority of cases of hydatid mole is false and should be discontinued. Curettage is preferable to hysterotomy in the treatment of hydatid mole. Hysterectomy and/or oophorectomy has no place in the treatment of hydatid mole. Chorioepithelioma, occurring several years following hydatid mole or pregnancy, is the result of an intervening abortion which has not been recognized.

Biologic pregnancy tests have not yet attained their proper place in the diagnosis and prognosis of hydatid mole and chorioepithelioma. Both positive and negative pregnancy tests should be repeated and verified in cases of hydatid mole and chorioepithelioma. Sufficient attention is not paid to the presence of lutein cysts of the ovary accompanying hydatid mole and chorioepithelioma. Oophorectomy is not necessary in the treatment of chorioepithelioma. Pulmonary metastases are the greatest single cause of death in chorioepithelioma.

CHARLES BARON, M.D.

GENITOURINARY SURGERY

ADRENAL, KIDNEY, AND URETER

Tubulointerstitial Extravasation. F. A. Reuter. *J. Urol.*, Balt., 1947, 58: 97.

Anuria following shock, injuries, operations, toxemias, and many other conditions, has been described in the medical literature. It may occur within a few hours of the insult or be deferred for several days. The pathogenesis is not well understood. Hemoconcentration, vasospasm, and renal anoxia are mentioned among the predisposing causes. The deposit of hemoglobin compounds in the tubules is prominently mentioned. The renal phase has been spoken of as tubular anuria, shock anuria, tubular nephrosis, and lower nephron nephrosis. In occasional cases, the patient recovers with medical treatment. An increasing number of patients are being reported to have recovered following renal decapsulation.

In most instances, whether the kidney is seen at operation or at necropsy, it is reported to be larger and of a weight considerably in excess of normal; it is pale, and the capsule is tense and strips with ease. The cut edges of the kidney evert and the renal tissue appears to be wet and edematous. Most authors have placed the renal lesion in the distal segment of the nephron. The pathology chiefly involves the tubule cells. These cells exhibit graded degeneration from simple cloudy swelling to areas of frank necrosis. Tubule dilation is not striking and a variety of casts and cellular débris appear in the lumina. The interstitial tissue is edematous. The glomeruli exhibit minimal damage, if any at all. There is every indication that filtration is not entirely suspended.

JOHN A. LOEF, M.D.

Comparison between Sodium Thiosulfate and Phenolsulfonphthalein Excretions. W. E. Goodwin. *J. Urol.*, Balt., 1947, 58: 151.

The recent work of Gilman and Newman indicated that the excretion of thiosulfate after the intravenous injection of sodium thiosulfate is a function of glomerular filtration. It is well established that the phenolsulfonphthalein test is a measure of tubular function. Since the thiosulfate test (because of its simplicity) is readily adaptable to clinical needs, the correlation between the two tests has been examined.

In 20 tests on 17 patients the thiosulfate (Nyiri) and phenolsulfonphthalein tests were carried out simultaneously. The author compares the results in an additional 10 cases in which thiosulfate clearances and phenolsulfonphthalein tests were done.

The results obtained confirm the work of investigators of 20 years ago, who found that the recoveries (per cent) of thiosulfate and of phenolsulfonphthalein in the urine after intravenous injection of the two substances are comparable and that the use of both are good tests of renal function in healthy and diseased kidneys.

The thiosulfate test has no clinical advantages over the phenolsulfonphthalein test, which is simpler and just as reliable an estimate of "total" renal function.

In carrying out the thiosulfate test, there is no particular advantage in collecting divided specimens, as two hour totals give the desired information.

The phenolsulfonphthalein test still stands as the most simple, accurate, and useful single clinical test of renal function in health and disease.

JOHN A. LOEF, M.D.

Traumatic Rupture of the Kidney. Seven Observations (Ruptura traumatica del riñon. A proposito de 7 observaciones). **Alfredo Pierini.** *Rev. As. méd. argent.*, 1947, 61: 404.

Pierini reports that 5 of his patients had complete renal rupture with a large perirenal hematoma and were submitted to nephrectomy. One of them died because surgical intervention had been delayed for 3 days; 2 had renal contusion without a palpable hematoma but with hematuria and were given medical treatment; they were cured without late complications.

Among surgeons there is now a tendency toward the expectant or conservative surgical method of treatment, nephrectomy being used for desperate cases, such as those with clinically important local hemorrhages and abundant, persistent hematuria, and with complete ruptures of the renal parenchyma with involvement of the calices, pelvis, ureter, or large vessels.

When intravenous urography can be used, as in most cases of closed traumatism, it reveals in a few minutes the anatomic and functional condition of the uninvolved kidney and provides information regarding the traumatized organ which permits the diagnosis and determination of the treatment to be applied. However, it is well to remember that temporary post-traumatic partial or total abolition of renal function may modify the excretion of the medium, and prevent the urogram from giving a true picture of the condition of the kidney; nevertheless, in most cases the excretion of the medium is sufficient to furnish images which are useful for the diagnosis. The clearest urographic films are obtained from 12 to 24 hours after the traumatism.

The most characteristic roentgen signs of a renal lesion are: (1) disappearance of the renal contour and of the border of the psoas muscle because of the presence of perirenal hematoma (when the hemorrhage is very abundant, it may produce a diffuse shadow in the renal area); (2) lumbar scoliosis and intestinal meteorism; (3) deformity or filling defect of the renal pelvis, with or without perirenal hematoma; (4) absence or filling defect of one or more calices, due to rupture, edema of the parenchyma, or intrapelvic coagula; (5) dilatation of the renal pelvis

by obstruction of the ureter with coagulum; (6) median displacement of the upper part of the ureter; (7) spilling of the contrast medium outside the pelvis and renal parenchyma because of their rupture; (8) a negative image through lack of elimination of the medium, which would suggest a grave lesion of the parenchyma; and (9) pleural effusion and decrease in the movements of the diaphragm on serial examination during the subsequent days.

Retrograde pyelography may be contraindicated by the seriousness of the clinical picture; in addition, it may increase the hemorrhage and carry infection to the kidney. Cystoscopy, pyelography, and the indigo carmine test to study the function of the opposite kidney should be used only in mild and average cases which are kept under observation in a specialized milieu. In an emergency service attended by general surgeons, intravenous urography constitutes a minimal requirement and should be omitted only in exceptional cases.

The expectant method should be reserved for minimal local and general pictures which represent closed lesions of the type of simple contusions or small parenchymatous fissures without rupture of the capsule, calices, or pelvis. Descending urography showing the absence of extravasation of contrast medium will militate in favor of expectation, as will also congenital absence of the opposite kidney even in the presence of persistent hemorrhage.

When the acute clinical picture demands it (frank anemia, hypotension, hematuria, palpable hematoma), after treatment of shock and, if possible, intravenous urography, exploratory lumbotomy is performed, or laparotomy when associated lesions are suspected. Without going to the extreme of conservation at all cost, the kidney must be respected if there is any possibility of functional recovery; even cortical lesions reaching the calices may be closed with careful sutures, preferably of ribbon gut (Lowsley and Menning), or including a piece of muscle or fat in the line of suture to give it greater strength. In other cases it will be necessary to take recourse to partial resection, heminephrectomy, or even nephrectomy in the presence of a pathologic kidney.

When the conservative procedure is pushed too far and is used in extensive parenchymatous wounds, abundant scarring may later be responsible for serious complications which may reach obstructive hydronephrosis, calculus formation, pyonephrosis, perinephritis, and final atrophy of the kidney. But when the conservative method follows the classical indications and is used in fissures of the parenchyma even with reparable wounds of the pelvis, it is rewarded by immediate successful results and by absence of late complications.

Nephrectomy, the operation of choice, gives the best immediate and late results. It is indicated in great destructions of the parenchyma, detachments of the pedicle, and irreparable lesions of the pelvis and/or ureter. In open lesions from cutting instruments or firearms with abdominal or lumbar injury, surgical intervention is indispensable as soon as shock has been overcome. The operation may or may not be started with a laparotomy to attend to the associated intestinal, hepatic, or other lesions, and the kidney may be approached through the same incision or through lumbotomy. In wounds from cutting instruments it will often be possible to suture the parenchyma. Wounds from fragments of grenades or bombs, and the presence of pieces of clothes and of soil in the tissues will indicate immediate débridement, resection of the tract, removal of the foreign bodies, and treatment of the renal lesion.

RICHARD KEMEL, M.D.

Contribution to the Diagnosis and Treatment of Papilloma of the Renal Pelvis (Ein Beitrag zur Erkennung und Behandlung des Nierenbeckenpapilloms). **Kurt Tzschirntsch** *Deut. med. Wschr.*, 1947, 72: 442.

Papilloma of the renal pelvis is extremely rare. According to European and American statistics, its incidence is about 0.65 per cent among all kidney tumors. Only 200 cases have been published in the entire literature. Histologically and biologically it is closely related to warts. Patients with papillomas of the urinary tract often also reveal papillomas of the skin.

The main clinical symptoms are hematuria and pain which in most cases occur in attacks, starting and stopping abruptly. It is difficult to make the correct diagnosis prior to surgery and to differentiate the papilloma clinically from other forms of pathology in the kidney pelvis (parenchymatous tumors, calculi). However, the diagnosis can be established if tumor tissue is found in urine obtained by catheterization of the ureter. Also, when villi from the papilloma are found in the voided urine, and cystoscopy reveals the absence of papillomas in the bladder, the diagnosis is certain. It has been shown that villi from the diseased portion can get into the healthy kidney by reflux and thus may cause diagnostic errors as to the site of the tumor. The most valuable help in the diagnosis is retrograde pyelography, especially in early cases. Later on, when hydronephrosis or pyonephrosis has developed, the filling defects fail to show up in the pyelogram. However, the pyelogram is not infallible. Very small papillomas may be overlooked, or soft calculi or coagulated blood may be mistaken for tumors.

The only effective treatment is surgery. The author is opposed to pyelotomy or nephrotomy because of the danger that very small papillomas may be overlooked. Moreover, the risk of dissemination and carcinomatous degeneration of the papillomas due to the operation is so great that conservative surgery is not justified. The only safe treatment is nephrectomy plus ureterectomy. The ureter should be removed in its total length, including the intramural portion in the wall of the bladder. Recurrences and metastases in the ureter, probably by way of implantation, have frequently been observed.

The prognosis is not altogether good, even in cases in which surgery was done at an early stage. The

question of malignancy in this seemingly benign tumor has been a subject of discussion for a long time. In 1924, Scholl of the Mayo Clinic reported 8 cases which were malignant clinically and histologically. Primary malignancy or secondary carcinomatous degeneration is estimated to occur in about 70 per cent of the cases. Recurrences and metastases occur usually within the first 3 years after surgery; late metastases seem to be rare.

The author reports a case of his own observation which was correctly diagnosed by retrograde pyelography. WERNER M. SOLMITZ, M.D.

A Clinical and Pathologic Anatomical Study of Tumors of the Kidney in Children, Based on a Series of 18 Cases. Eino E. Vuori. *Acta chir. scand.*, 1947, 95: 555.

The author reports 18 cases of tumors of the kidney in children from 2 months to 8 years of age. These cases are all from hospitals in Finland and none has previously been reported.

The first symptoms were listlessness, anorexia, weight loss, anemia, slight fever, and, rarely, hematuria. In 17 children the tumor was discovered on admission. The period of time which had elapsed between the first appearance of symptoms and the diagnosis was from 1 day to 10 months, the average being 4 months. Wrong diagnosis, or failure to discover the tumor, occurred once in 4 patients, twice likewise in 4 patients, three times in 1 patient and four times also in 1 patient. The time lost in this way was from 21 days to 10 months. The author stresses the rare, and late, metastases from these tumors and the late breakthrough of the renal capsule, and encourages earlier diagnoses through an awareness of this disease on the part of those who treat the diseases of children.

In the author's series, nephrectomy was done transperitoneally in 5 patients, and retroperitoneally in 13. He favors the former method as it allows for ligation of the renal vein before mobilizing the tumor.

Nine patients were given postoperative x-ray therapy, but all died of recurrences. Of the total series, 14 patients died of recurrence within the first 16 months after operation; 4 patients are still living after 18 months, but 1 patient has already been found to have recurrence.

The tumors included both the nodular and solid, as well as the smooth and pasty variety. Histologically they were of widely different types, ranging from the most primitive sarcomatous forms to adenomatous varieties containing glomerular elements. The so-called capsule is regarded as a sclerosed layer of renal tissue. JOSEPH E. MAURER, M.D.

Primary Carcinoma of the Ureter. J. M. Hundley and J. S. Hunter. *J. Urol.*, Balt., 1947, 58: 176.

The authors present a case of carcinoma of the ureter to illustrate the danger of referring to a lesion as "benign papilloma of the ureter" and emphasize that such a lesion is not benign either clinically or pathologically and must be considered a malignant tumor.

The lesion is most common in the sixth and seventh decades and occurs in the male more often than in the female. The usual symptoms are hematuria, pain, and a tumor mass. Pathologically, primary carcinoma of the ureter is either papillary or nonpapillary, and spreads early and more extensively than a similar lesion of the bladder. Ureteronephrectomy with segmental cystectomy as an extraperitoneal one stage operation is the procedure of choice.

The case presented was that of a 56 year old white female who was admitted to the University Hospital, Baltimore, Maryland, complaining of hematuria for a week. A retrograde pyelogram showed no filling of the left ureter or kidney, although the bleeding was from the left ureteral orifice. Nephrectomy and ureterectomy was done, but the lower portion of the left ureter was not removed, as it seemed to be uninvolved. The microscopic picture was that of "benign papilloma of the ureter." Three months later cystoscopy revealed a growth projecting from the left orifice. The lower segment of the ureter was then removed, and a large tumor was found. A recurrence at the lumbar incision was found also. The patient died 6 months after the nephrectomy because of the recurrence and metastases.

JOSEPH E. MAURER, M.D.

BLADDER, URETHRA, AND PENIS

Visco-Rayopake in Cystourethrography. C. E. Richards. *J. Urol.*, Balt., 1947, 58: 185.

Cystourethrography is a valuable diagnostic procedure which has not been generally used because of technical difficulty and because there has been no entirely satisfactory medium. The author presents his experiences with a new water soluble viscous radiopaque substance, visco-rayopake, which he believes is safer and more efficient than any contrast media previously proposed for urethrography.

The cystourethrogram is helpful in the diagnosis of any condition which produces gross anatomic alteration in the contour of the bladder or the urethra. It is an adjunct to the usual procedure of urethroscopy, and in cases in which the passage of an instrument is impossible it may be the only approach to an accurate diagnosis of the presenting condition. Its outstanding advantage over cystourethrography is that it provides a permanent graphic record and may, on comparison with later similar studies, be invaluable in evaluating the progress of the condition under consideration.

A cystourethrogram is a roentgenogram of a bladder and urethra whose outlines have been made apparent by the presence within their lumina of a radiocontrast medium. A 2 to 7 per cent solution of sodium iodide is an entirely satisfactory medium when an opaque cystogram is desired. The search for a satisfactory medium for urethrography has not been so successful. Such a medium must possess all

the attributes of the ideal cystographic medium, but it must, in addition, be somewhat more radio-opaque and also considerably more viscous. The necessity for increased radio-opacity is due to the fact that x-rays, in passing through the urethra, are interrupted by such a relatively shallow column of the contrast medium that, to produce a satisfactory roentgenogram, this thin layer of medium must be almost totally opaque to the rays at the required exposure. Also, the changes in structural pathology encountered in this region are frequently so delicate that the urethrogram must have an exceedingly sharp and detailed outline demonstrating the most minute anatomic abnormality.

The necessity for increased viscosity is due to the fact that, when at rest, certain segments of the normal urethra are occluded by the sphincters and the pressure of the surrounding tissue. To completely visualize these segments on a roentgenogram it is necessary to expose the x-ray film while they are temporarily opened by the flow of an opaque medium through their lumina. This may be accomplished either by voiding the medium from the bladder or by injecting it retrograde through the urethral meatus at the time of exposure. However, for the column of opaque material which is passing relatively slowly through these segments of the urethra to open them sufficiently to produce a satisfactory outline, the opaque material must have a viscosity many times that of ordinary aqueous solutions.

Up to recently, the substances which were most frequently used for urethrography contained some type of an iodidized oil. They had a tendency to be somewhat irritating to the mucosa of the urethra, due to free iodine being liberated from the compound when exposed to air, light, or high temperature. Furthermore, having an oil base, there were certain inherent disadvantages to any nonwater-soluble agent inasmuch as they are not miscible with the urine and sometimes produce an irregular outline due to globules of the dye mixed with the urine or aqueous cystographic medium. The most serious objection to the iodized oils is the possibility of introducing some of the medium into the general circulation, producing a fat embolus.

Visco-rayopake is an experimental organic iodide developed recently as a radiocontrast medium. It seems to be a substance which meets every requirement for the perfect urethrographic contrast medium. It is more viscous than any of the previously proposed media. It produces sharper outlines and better detail than any other, except perhaps the iodized oil. It seems to possess all the advantages of the iodized oil and at the same time has none of their potential dangers and disadvantages. It is water-soluble and therefore miscible with urine and aqueous cystographic media. Most important of all, its use carries no risk of fat embolus or general systemic defect even if it should inadvertently be introduced into the circulation during urethral injection. The authors have used visco-rayopake in 54 patients with excellent results. They have experienced no evidence of local or generalized irritation or toxicity, nor has there been anything suggestive of an allergic phenomenon. There have been no reports in the literature of any type of serious reaction to this substance.

The author outlines the usual procedure for making cystourethrograms, as follows:

1. Adequate preparation of the patient with purgatives and enemas.
2. The patient empties his bladder as completely as possible.
3. A plain x-ray of the abdomen is made.
4. A small soft rubber urethral catheter is introduced into the bladder and the residual urine, if any, is measured.
5. A 2 to 4 per cent solution of sodium iodide is introduced into the bladder, the amount and the concentration varying with the circumstances.
6. The catheter is withdrawn, leaving the iodide solution in the bladder.
7. With the patient in the supine position, 25 c.c. of visco-rayopake is injected slowly into the urethra, the last 5 c.c. during the exposure of the film. Having the patient relax completely and attempt to void, facilitates this injection by opening the external urethral sphincter. The x-ray tube is centered directly over the symphysis pubis.
8. With the urethral meatus occluded, the patient turns on his side so that the pelvis is at a 45 degree angle to the vertical plane, the lower thigh and leg in complete flexion, and the upper thigh and leg in complete extension. A film is exposed in this oblique position during the injection of an additional 5 c.c. of contrast medium.
9. The patient voids. If there is more than 50 c.c. residual left in the bladder, a catheter is passed at the end of the procedure to remove the remaining sodium iodide solution.

In a large majority of patients, these two views will give all the desired information. If a very sharp outline of the bladder is desired, a more concentrated solution is used. If a bladder-filling defect is suspected, such as an enlarged prostate, neoplasm, or nonopaque calculus, then a less concentrated solution is indicated. If one is interested primarily in delineating the bladder outline, a maximum amount of solution should be instilled. If one is looking for encroachment on the bladder's lumen, a smaller amount of solution would be instilled.

The author concludes that visco-rayopake is believed to be the safest and most efficient urographic contrast medium yet produced.

ROBERT O. BEADLES, M.D.

Carcinoma of the Bladder. James T. Priestley. *J. Am. M. Ass.*, 1947, 134: 507.

Many factors must be considered in deciding on the most desirable type of treatment for a patient who has carcinoma of the bladder. These include the size, grade, and location of the lesion, the degree of infiltration, whether the lesion is single or multiple, whether the ureterovesical orifice is involved on one or both sides, the status of renal function, the

age and general condition of the patient, and the risk and prospect of cure afforded by various available procedures. It should be remembered that even the most capable cystoscopist is subject to the inherent limitations of all transurethral procedures in treating a vesical carcinoma through the cystoscope. It is thought that in general the treatment of vesical neoplasm has been too conservative in type. External irradiation is not a primary treatment of choice.

The principal suprapubic procedures employed in the eradication of vesical neoplasm are electroexcision and fulguration, with or without the simultaneous implantation of radon, segmental resection (in rare cases local excision) and total cystectomy. Segmental resection seems satisfactory for a limited number of properly situated growths. Total cystectomy is in the process of being re-evaluated and it is thought that its field of usefulness is broader than has been appreciated in the past. Bilateral ureterosigmoidostomy, which can be performed in most cases of vesical neoplasm, is considered the desirable form of diversion of the urinary flow in association with total cystectomy.

Primary Carcinoma of the Male Urethra. W. E. Lower and K. F. Hausfeld. *J. Urol.*, Balt., 1947, 58: 192.

The authors have reviewed the literature since 1941 and have found 8 new case reports on carcinoma of the male urethra, which, added to Wishard's report and resumé, made in May 1941, plus 10 cases from the Cleveland Clinic and presented in the present report, brings the total number of cases of carcinoma of the urethra, which appear in the literature, to 192. The 10 case reports included in this article are complete résumés and should be studied.

The authors conclude, from their study of the literature and from the case reports presented, that the clinical manifestations of carcinoma of the male urethra are often incorrectly interpreted. Too often treatment is directed to the stricture or the complications, such as rupture of the urethra with perineal abscess and urinary fistula. Hence, when the true condition is discovered the malignant process has spread beyond its local origin and treatment is no longer effective. They suggest that any progressive difficulty in urination (especially when associated with a periurethral mass or the onset of a rather sudden marked difficulty in dilatation of strictures which have been treated by instrumentation for some time) should immediately suggest the possibility of malignant disease of the urethra, and if the diagnosis is made early, extensive resection of the urethra would seem the treatment of choice. In certain selected cases the condition would probably respond to radiation.

ROBERT O. BEADLES, M.D.

Paraffinomas of the Penis (Des paraffinomes de la verge). **Jean Quénu and Étienne Pérol.** *J. chir.*, Par., 1947, 63: 345.

Injuries caused by subcutaneous injection of paraffin or vaseline for cosmetic purposes have been reported frequently in the literature. However, only 5 cases are on record in which the injections and the resulting lesions were in the penis. The purpose of these injections, performed either by the patient himself or by another person, was to increase the volume of the organ. The amount of the liquid injected varied between 20 and 80 c.c. The injections are not particularly painful and are followed rapidly by considerable edema which makes sexual relations impossible. Later on, the deposits of paraffin in the subcutis are encapsulated by proliferation of the fibrous tissue. This connective tissue reaction may produce widespread fibrous infiltrations so that the entire organ becomes surrounded by a sclerotic shell of fibrous tissue which makes erection impossible. In addition, inflammatory reaction may occur with formation of sterile abscesses, ulcerations, lymphangitis, and involvement of the regional lymph nodes. The glans as well as the cavernous bodies are never involved. The prepuce may acquire huge dimensions and give rise to phimosis or paraphimosis, or it may become necrotic and be destroyed. The principal site of the lesions is the subcutaneous tissue of the trunk of the penis. Here, the sclerotic shell may reach a thickness of several millimeters; it is of firm elastic consistency like the musculature of the thigh, at places as hard as cartilage. The skin shows discoloration to a waxy white or yellow. Since the paraffin migrates along the lymphatics, the infiltration may not be limited to the penis but spread into the scrotum, the perineum, and the pubic region. Ulceration and the formation of sinuses occurred in only 1 of the 5 cases. The course varied considerably, not only in kind and extent of the lesions but also in time. In the 5 cases the lesions began to show from several months to 10 years after the injection.

To these 5 cases the authors add a sixth of their own observation. A man of 45 years was seen for lesions at the dorsal and lateral aspects of the penis, which had developed very slowly in the course of 7 years. The patient gave the history that the condition started with 2 small not tender nodules at the sides of the penis which later became confluent. Only 6 years later the skin broke and ulceration developed. A biopsy confirmed the diagnosis of paraffinoma. At this time the trunk of the penis proximal to the normal glans was reduced to almost nothing and had retracted to the pubic region. The entire dorsal and a large part of the lateral aspects formed one large ulcer with a pink indurated base and irregular hard borders. The surrounding integument was glossy, smooth, of firm consistence, and purplish in color. The infiltration extended beyond the root of the penis to the region of the symphysis and down to the scrotum. The inguinal nodes were hard, the size of hazelnuts, and not tender. A biopsy taken from the inguinal nodes showed that the normal follicular arrangement had disappeared almost completely. The lymphoid tissue was largely replaced by strands of fibrous tissue and by a great number of nodules of epitheloid cells, interspersed

with a certain amount of giant cells. These nodules resembled tubercles; however, no trace of caseation was found. Furthermore, the giant cells were not of the Langhans type with horseshoe arrangement of the nuclei; rather they resembled foreign body giant cells, their nuclei being arranged more to the center of the cell. Closer investigation revealed that the cytoplasm of the giant cells as well as the epithelioid cells contained numerous small droplets of a fatty substance which obviously was paraffin. Similar findings were revealed in a later biopsy from the edge of the ulceration.

In a series of 6 interventions, the paraffinoma was excised and a penis of normal length and shape formed by transplantation of skin from the pubic region. The result was satisfactory from the anatomical as well as the functional point of view.

It should be mentioned that the patient consistently denied ever having had an injection of paraffin; however, in view of the histological findings, there could be no doubt about the diagnosis.

WERNER M. SOLMITZ, M.D.

GENITAL ORGANS

Some Observations on Transurethral Prostatic Resection. Reed M. Nesbit. *N. England J. M.*, 1947, 237: 207.

The author emphasizes certain details of technique that have been found necessary to the successful execution of transurethral resection. This operation has been performed in the University of Michigan Hospital at Ann Arbor, since October, 1931, and experience has shown that prostatic resection possesses many attendant hazards and that there are numerous pitfalls in the performance of this technically difficult operation. Most of these can be considered under trauma and hemorrhage.

One of the most frequent causes of immediate and late complications is urethral trauma. When the urethra is traumatized by forceful introduction of rigid instruments that are too large there results an introduction of infection manifested by the development of local tenderness of the urethra and general sepsis; later the development of stricture completes the cycle and may leave the patient with a lesion which is just as debilitating and infinitely more difficult to treat than prostatism. Urethral trauma is usually avoided if the surgeon does not introduce the standard size resectoscope into the urethra which fails to accommodate easily a No. 30 Fr. steel sound. When smaller urethras are encountered one may use a resectoscope having a sheath of smaller than standard diameter. If this is impractical, the surgeon has two procedures that can be followed: (1) meatotomy will often permit the passage of the resectoscope; however, in some cases the remainder of the urethra is too small and then perineal urethrotomy is indicated. At the University of Michigan Hospital, approximately 35 per cent of the patients operated on by resection require meatotomy, whereas perineal urethrotomy is performed in 20 per cent.

Other indications for perineal urethrotomy include: (1) severe urethritis; (2) shortness of the penile suspensory ligament; (3) excessive length of the prostatic urethra; (4) abnormal position of the prostatic gland. In performing resection on large glands, that is, those in which 50 gm. or more of tissue is removed, urethrotomy is used in 30 per cent of the cases, in comparison to 20 per cent of all cases. In the resection of large glands the procedure allows an increased maneuverability that has facilitated the technique of operation.

It can be accepted as an axiom of transurethral surgery that the resectoscope must be freely and easily contained by the urethra at all times. Single exception to this rule is when the instrument is held tightly in the prostatic urethra by cancer or by contracture of the vesical neck. Whenever perineal urethrotomy is indicated to effect this purpose, it should be done, for it is simple to perform and the patients suffer little or no inconvenience from it. They rarely pass urine through the incision, and none develops stricture at the site of operation.

Another form of trauma occurs when the resectionist cuts too deeply into vulnerable areas. The most frequent are perforation of the prostatic capsule and injury of the external urinary sphincter. Minor perforations rarely give rise to morbidity and are probably of little clinical significance. Healing of the defect probably takes place quite rapidly and is enhanced by the catheter diversion of the urine. Extensive perforation, however, may give rise to pelvic cellulitis and extravasation, and, if not recognized and promptly treated by adequate drainage, will terminate fatally.

Urinary incontinence following resection occurs when the external sphincter is cut with the resectoscope and is a complication which can be avoided, even by the inexperienced resectionist, if due care is exercised in the performance of a sound technique. Except in the presence of infiltrating cancer or inflammatory contracture that involves the membranous urethra, the proximal margin of the external sphincter can be recognized by certain anatomic properties of the structures that go to make up the area. The membranous urethra is an immobile structure, whereas the adjoining prostatic urethra is slightly mobile, but the mucosa of each structure is tightly adherent. When the prostate gland is moved, the surface configuration at the prostatomembranous juncture is altered by wrinkling in a manner comparable to the wrinkling of the bellows that connects two Pullman cars. The mucosal folds that are created in this manner are transversely disposed and extend around the entire circumference of the urethra. They can be recognized easily when observed through the resectoscope and are brought into view most effectively if the instrument is moved in and out through a short excursion while the area is being inspected. Fortunately, this wrinkling phenomenon tends to increase as the transurethral resection progresses because of the increased mobility of the gland that is effected by the operation, so that the surgeon can al-

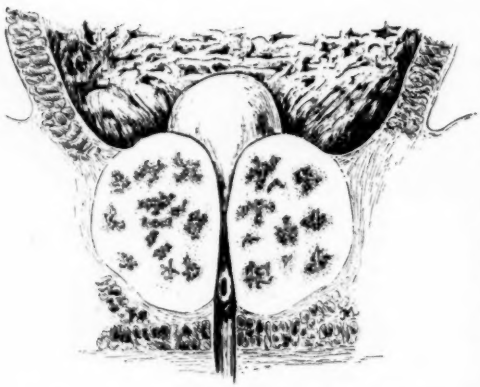

Fig. 1. Diagram showing obstruction at bladder outlet produced by hypertrophy of two lateral lobes and median lobe of prostate.

ways demonstrate the prostatomembranous junction toward the end of the operation and can safely excise tissue down to that point without fear of sphincter damage.

Hemorrhage. Every prostatic resection is accompanied by blood loss, and it is important that the surgeon have more or less accurate information regarding the amount of blood loss. A method of estimation of blood loss was described by the author in 1941, and provides the surgeon with objective data regarding the patient's need for replacement therapy.

The successful control of bleeding during the operation depends on certain details of technique which are acquired with experience. Bleeders are easily recognized and quickly arrested when the walls of the prostatic fossa are smooth and clean, for then the resectionist is able rapidly to survey the entire operative field from a vantage point at the membranous urethra; but when the operative field is irregular and has an uneven surface, bleeding points are not readily seen and the roughness of the irregular surface tends to increase the difficulties by enhancing the formation of blood clots, which in turn conceal underlying bleeders. The experienced resectionist strives to make each excursion of the cutting loop extend the full length of the adenomatous mass that is being resected. When long masses of tissue are to be excised the operator, while cutting, may slide the sheath of the instrument toward himself with the loop extended, so that longer slices of tissue than would otherwise be permitted by the full excursion of the loop can be excised. When the distal end of the adenomatous mass comes into view, the movement of the sheath is stopped, and the cutting loop is pulled forward and finally appears within the sheath, shearing off the fragment. The instrument is then kept in place while the tissue fragment floats away in the stream of water flowing through the sheath, permitting an unimpeded view of the excavation, and the operator can either arrest bleeding within the excavation or continue to carry out his cutting maneuvers. By a technique of this sort, the cut surface can be kept smooth and free from bleeding points and blood clots during the operation.

The injection of various vasoconstrictive substances into the prostate gland to lessen the amount of bleeding during operation is not recommended.

Postoperative control of bleeding presents another problem, and it was formerly the practice of the author to irrigate the bladder with water every 10 or 15 minutes during the first 24 hours after operation. In the past 2 years this was replaced by the instillation of thrombin into the prostatic fossa and the discontinuance of postoperative irrigation. After running comparative series, it was found that the elimination of irrigations was the factor of greatest importance in controlling the postoperative bleeding. Consequently, at this time they use no thrombin and do not irrigate after resection. With this régime there have been fewer cases of catheter blockage than ever before.

Operative Technique. The author presents a short résumé of the technique that has been successfully employed in prostatic resection. In this procedure there are three phases of operation: in the first, a cone of tissue is removed—the apex of the cone is at the apex of the prostate, and the base of the cone is encircled by the internal vesical sphincter; the second phase consists of removal of the remaining lateral lobe structures from within the concave prostatic fossa; and the third phase consists of careful removal of the apex masses touching the external sphincter.

In the first phase the resectoscope is rotated so as to enable inspection of the anterior wall of the prostatic urethra. The anterior commissure is observed, and one of the masses of the lateral lobe is often found to bulge more prominently than the other into the field of vision. This one is chosen for the beginning of the operation. The extended cutting loop is brought into contact with the cephalad end of the lobe just lateral to the commissure and is drawn forward along with the resectoscope, and a fragment of tissue extending the full length of the lateral lobe mass is excised and allowed to float into the bladder. The observation of tissue morphology during the operation is of primary importance for it is only in this manner that the surgeon is guided in determining what should not be excised. The tissues of the adenomatous mass have a characteristic appearance that varies only when there is excessive leiomyomatous stroma. The appearance of the compression capsule is different from that of either the normal or adenomatous prostate gland. It has a sort of asbestos appearance when viewed through the foreobliquelens system. Infiltrating cancer is identified by its cellularity. The internal sphincter is easily recognized by its circular muscle fibers, and the prostatic capsule has a fibrous appearance that facilitates identification.

During resection, if only prostatic tissue is identified in the initial furrow, another fragment of tissue

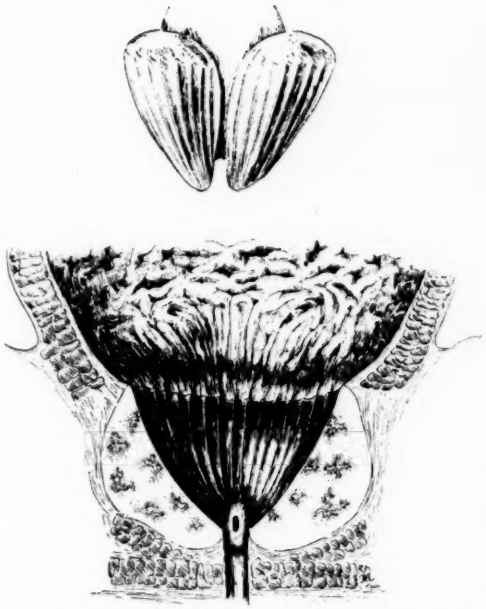

Fig. 2. Diagram showing cone-shaped area left after first phase of operation has been completed. Although a large part of the median and lateral lobes has been removed, there still remains much prostatic tissue to be removed from concave prostatic fossa.

can safely be excised in the same line, but if muscle fibers are recognized at the inner end of the furrow, the operator must cut no deeper at that point. Instead, the resectoscope is rotated a few degrees laterally so as to begin its next excision of tissue fragment. This slice of tissue and each successive one extend, like the first fragment, the full length of the gland, and the furrow that is formed by the second cutting stroke is confluent with the first, and, like the first furrow, is deepened until circular fibers of the internal sphincter are encountered; then the resectoscope is again rotated a few degrees, and another adjoining furrow is made. It is noteworthy that each of the successive cuts exposes a small arc of internal sphincter but that the individual furrows extending toward the apex of the prostate converge at a point, for the membranous urethra is a fixed point. The confluent furrows that successively expose the circumference of the internal sphincter create a cleft extending from that circle out to the apex, and the cleft that is created in the manner described often encircles sizable masses of prostate. These masses are composed of portions of the lateral lobes and of the median lobe, and when encircled as described and cut off from the peripheral circulation the entire mass can be cut up into fragments quickly and bloodlessly. In the resection of small obstructing glands or contractures, the cutting maneuvers in the first zone of operation often entail only the removal of a shallow depth of tissue, so that there may be no encirclement of a tissue mass. When the first phase of operation has been concluded, there is a cone-shaped space extending from the apex of the gland to the circle described by the internal vesical sphincter. The walls of this cone are smooth and are composed of prostatic tissue, and any bleeding points are easy to identify.

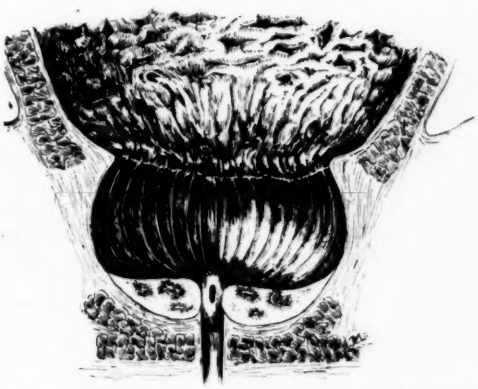

Fig. 3. Diagram showing how prostatic tissue is removed from concave fossa down to capsule of prostate. At conclusion of this second phase of operation there remains only some prostatic tissue at apex of gland adjacent to and just above external voluntary sphincter muscle. In the third stage of operation this remaining tissue at apex of prostate gland is removed.

The second phase of operation is concerned with the removal of adenomatous tissue from the concave prostatic fossa. In this zone the cutting loop enters the prostatic mass distal to the circular fibers of the internal sphincter, and each excursion of the loop extends almost to the external sphincter, where a small mass of tissue is allowed to remain as a bulwark against injury of the sphincter. In this zone the first cut is made anteriorly, and successive cuts are made in the same furrow until the capsular structures are recognized. Successive cuts are made lateral to the original furrow until capsular structures come into view, and dissection is continued with the object of creating a cleft that is peripheral to the adenomatous mass of tissue. Digital palpation of the gland during the resection within the posterior half of the fossa is essential to accurate and safe dissection. With a finger in the rectum the surgeon is able to palpate quite accurately the thickness of the adenoma and, when nodular masses are relatively inaccessible because of unusual position, to push them upward into the path of the cutting loop. By peripheral dissection in the second zone of operation the adenomatous mass is devascularized so that the free mass that is finally isolated on the floor of the urethra can be expeditiously and safely excised by rapid resection.

At the conclusion of the second phase of operation, the surgeon is able to view the entire fossa from the vantage point at the apex of the gland. In the distance he can see the denuded internal sphincter, and in the foreground he is able to inspect the smooth, concave walls of the prostatic fossa. Bleeding points are readily discovered.

The final phase of operation requires a meticulous and careful dissection, for it is now that the surgeon resects all tissues down to the margin of the external sphincter. This margin is readily identified, as described above, by observation of the transverse fold or wrinkle that is made visible when the resectoscope is moved in and out and rotated while the area in question is inspected. When the outer margin of safe resection has been delineated throughout its entire circumference, the excision of apical tissue can be carried out as far as this line. The resection is started anteriorly; the instrument is then rotated as successive adjoining fragments of the gland are excised until the ejaculatory ducts and the verumontanum are reached, but these structures are not removed. Although the apex of the adenomatous gland is tapered in form and ends at the triangular ligament, it often extends laterally for some distance on this abutment, and resection at the apex must extend not only down to the urethral level but also deeper on each side of the midline so as to include the removal of all adenomatous tissue contained within the capsule. This is greatly facilitated by rectal palpation.

By employing a systematic approach in the technique of transurethral resection the urologist is enabled to perform a subtotal removal of the prostate gland, and the size of the gland that is removed depends in a large measure on the factors of dexterity and experience in the performance of the operation. The author cautions that subtotal prostatectomy is essential to the attainment of consistently good results, and when this objective cannot be attained by the urologist it would be well to treat the patient by some enucleative procedure, for the cure of prostatism depends on the extirpation of the gland.

ROBERT O. BEADLES, M.D.

Spontaneous Torsion of the Testicle (Torsione spontanea del testicolo). **Mario Ballestrero.** *Arch. ital. chir.*, 1947, 69: 73.

In a series of 18 cases of spontaneous torsion of the testicle seen between 1935 and 1945, the author found the greatest frequency between the ages of 15 and 25.

An acute onset of pain and prostration of the patient with swelling of the scrotum and a fixed testicle are significant for the diagnosis of torsion of the testicle. Transillumination and the finding of bloody serous material with an explorative puncture needle confirms the diagnosis.

Torsion, if left alone, will cause atrophy of the testicle. Although spontaneous detorsion is possible, it is an infrequent occurrence. The vitality of a twisted testicle ranges between 12 and 16 hours. The earlier the intervention, the better the prognosis will be.

Manual detorsion may be attempted but is not practical; one must resort to surgery as the only sure way to correct this condition.

ARTHUR F. CIPOLLA, M.D.

SURGERY OF THE BONES, JOINTS, MUSCLES, TENDONS

CONDITIONS OF THE BONES, JOINTS, MUSCLES, TENDONS, ETC.

Contribution to the Study of Eosinophilic Granulomas and Their Relation to Bony Xanthomas (Contribución al estudio del denominado "granuloma eosinofílico" y a sus relaciones con la xantomatosis ósea). **Fritz Schajowicz and Moisés Polak.** *Rev. As. méd. argent.*, 1947, 61: 218.

The authors maintain that the difficulty in classifying tumors of the reticuloendothelial system resolves into a lack of exact diagnosis, particularly by biopsy, which will enable one to determine: whether the lesion is inflammatory, hyperplastic, or blastomatotic; whether it is a reticulosarcoma or the relatively benign hyperplasia of the reticulohistiocytes; or whether one is dealing with the solitary granuloma of Otani and Ehrlich, the eosinophilic granuloma of Jaffe and Lichtenstein, or a solitary or multiple osseous xanthoma, the latter with or without the Schueller-Christian syndrome.

After citing the various factors, the authors believe that there is no fixed criterion for classifying these lesions. Some consider them independent entities; others, related conditions. Eight cases are presented. The studies were confirmed by small biopsy specimens in some instances and in others by abundant material obtained from more extensive surgical procedures.

It was concluded that the lesions were remarkably similar, and that the histiocytes are capable of forming fibroblasts or giant cells, can store lipoids, or may be accompanied by an eosinophilic reaction. Moreover, it was established that there is a relation between histiocytic granuloma, with or without eosinophils, the bony xanthoma, with or without the Schueller-Christian syndrome, and Letterer-Siwe's disease. The inflammatory factor as causation of these lesions is stressed. Classification of the reticuloendothelial hyperplasia is appended.

STEPHEN A. ZIEMAN, M.D.

Functional Aspects of the Abductor Muscles of the Hip. Verne T. Inman. *J. Bone Surg.*, 1947, 29: 607.

In order to explain the various clinical observations in instances of derangement of the abductor muscles, the authors made a study of the forces acting in and around the hip joint. The reacting force in the head of the femur resists not merely the pressure of the superincumbent body weight, but, in addition, the force of the abductor muscles and the tension on the iliotibial tract which is necessary to hold the pelvis in equilibrium. With the knowledge of the direction of the reacting force through the head and neck of the femur against the pelvis, the changing angle of the capital epiphysis during growth becomes partially explicable. Close inspection of roentgenograms of the upper end of the femur in individuals of various ages reveals that the epiphyseal line always lies at a right angle to the direction of the medial trabeculae of the femoral neck. Since the reacting force in the femur follows these trabeculae, there is no sheer on the epiphyseal cartilage. The only force to which it is subjected normally is a compressional one. As growth occurs, with increasing length of the femoral neck and increasing angle of pull of the abductor muscles and the fascia, the epiphyseal cartilaginous plate rotates so as to lie perpendicular to the equilibrant force in the femoral neck.

The interrelationship of these forces becomes altered in cases of paralysis of the abductor muscles and in congenital dislocation of the hip. In the first instance, the loss of muscle power prevents the attainment of equilibrium with the body in a normal position. To prevent the pelvis from rotating toward the nonweightbearing side, the individual shifts his center of gravity over the affected hip by bending to that side. The resultant forces acting through the hip become more nearly vertical. The equilibrant or reacting force in the femoral neck likewise shifts toward the vertical; the epiphyseal cartilaginous plate, remaining perpendicular to these forces, continues to be relatively horizontal, and coxa valga results. This is a constant finding in individuals who have had paralysis early in life, and the degree of coxa valga is in proportion to the loss of muscle power. Coxa valga occurs in individuals suffering from congenital dislocation of the hip, for the same factors are at work. In these cases, the loss of fulcrum prevents the normal development of the abducting forces. The load is borne vertically on the femur, and the capital epiphysis reacts by remaining horizontal. In malum coxae senilis, the bone changes affect predominantly the superior aspect of the femoral head, because the forces are concentrated there.

After the magnitude of the torque about the hip joint has been determined, as the center of gravity of the body lies medial to the center of rotation of the hip, it becomes possible to calculate the minimum pull of the abductor muscles and the amount of tension exercised by the iliotibial tract in counteracting this torque. Since the center of gravity necessarily lies in the median sagittal plane, the torque is the product of the body weight and the distance from the median sagittal plane to the center of rotation of the femoral head. The determination of the experimental values of the torque about the hip joint on the weight-bearing side was based upon myographic recordings. Both skin and needle electrodes were utilized. The electrodes were placed in or over the tensor fasciae femoris, the gluteus medius, and the gluteus minimus. The action currents were amplified by means of the Grass electroenceph-

alograph, and the output was passed through a voltage integrator to facilitate the estimation of the electric potentials. The action potential was obtained as the individual bore all his weight on the limb to which the electrodes were applied. The opposite extremity was flexed at the hip and the knee, just sufficiently to clear the floor. The abductors necessarily contracted to keep the pelvis level and the degree of contraction was recorded by means of the myograph.

It is quite apparent that when the subject is standing on one extremity with the pelvis level, the force which prevents the pelvis from rotating about the supporting hip is not due entirely to muscle pull. A considerable amount of force is contributed by passive tension on the fascia lata and the iliotibial tract. As the pelvis is depressed toward the nonweightbearing side, the fascial structures become increasingly taut and assume a greater and greater degree of tension until a point is reached where little or no muscle contraction is required.

C. Fred Goeringer, M.D.

SURGERY OF THE BONES, JOINTS, MUSCLES, TENDONS, ETC.

The Repair of Defects of the Radius with Fibular Bone Grafts. Richard C. Miller and George S. Phalen. *J. Bone Surg.*, 1947, 29: 629.

There are both advantages and disadvantages in the use of fibular grafts. The fibular graft has the advantage of providing considerable stability to the grafted bone. Furthermore, the fibula is approximately the same size as the radius so that ultimately, when healing is complete, the normal contour and probably the normal strength of the radius have been restored. Finally, the use of a fibular graft will avoid the infrequent, but ever imminent, complication of fracture through a tibial donor site. The primary disadvantage of the fibular graft is its relatively greater degree of density of cortical bone, as compared to that of tibial or iliac grafts. The osteogenic properties of the fibular graft are, therefore, not so great as those of a tibial or iliac graft. To obviate this disadvantage, it has been suggested that the drilling of multiple small holes throughout the graft might increase the vascularity and the rapidity of "take." This procedure had not been employed in any of the cases presented.

Over a period of 18 months, the authors treated 16 of these defects with fibular bone grafts. In general, the fibular grafts were 3 inches longer than the radial defects. This allowed for 1½ inches of onlay graft on each radial fragment. The distal end of the ulna was not resected in 5 of the 16 cases. In 3 of these 5 cases, rotation of the forearm has subsequently been greatly restricted. All of the patients in whom the distal end of the ulna has been resected have regained a satisfactory range of rotation in the forearm (more than 100 degrees), except one.

The authors found that the resection of the distal end of the ulna subperiosteally facilitated the bone graft operation. This procedure eliminated a later operation which would probably be necessary to restore rotation to the forearm and correct the radial deviation of the hand. In the authors' experience there has not been a great deal of difference symptomatically or functionally between the cases in which the ulna has been anchored to the flexor carpi ulnaris and those in which it has been left free.

The fibular graft is obtained from a normal leg, preferably that on the side opposite the fractured arm, to give the second surgical team more room in which to work. The fibular shaft is exposed subperiosteally through a lateral longitudinal incision, dissection being carried down along the posterior intermuscular septum between the peroneal and soleus muscles. Care is taken not to injure these muscles. A measured amount of fibula is then removed with a Gigli saw or osteotome. The length of the graft may be calculated before operation by adding 3 inches to the length of the radial defect. Proximally, as much of the fibula as desired may be removed; this may, if necessary, include the head of the bone. It is, of course, necessary to spare the peroneal nerve as it rounds the neck of the fibula. Distally, at least 3 inches of the fibula must remain to maintain the stability of the ankle mortise. In the forearm it was found best to employ a dorsal lateral incision. The superficial branch of the radial nerve is identified and protected throughout the operation. Dissection is carried down through the muscle planes, usually between the extensor carpi radialis longus and the brachioradialis, and the radial fragments are exposed subperiosteally for a distance of at least 1½ inches. Scar tissue and devitalized bone fragments are removed from the site of nonunion. The ends of both radial fragments are sawed back at right angles to the shaft until the sclerotic portion has been removed and good vascular bone is apparent. The graft is held in place by metallic fixation. In some instances, the distal fragment is so osteoporotic that screws will not hold, and in these cases 2 double strands of No. 22 tantalum wire have been used.

In this series infection occurred in 2 cases; in one case the purulent drainage had its onset 12 weeks after the operation, and in the other case it occurred 8 weeks postoperatively. Penicillin is administered for 1 day before operation and both penicillin and sulfadiazine are given for at least 6 or 7 days after operation.

C. Fred Goeringer, M.D.

Tendinous Reconstruction of the Hand following Irreparable Injury to the Peripheral Nerves and Brachial Plexus. C. A. Luckey and S. R. McPherson. *J. Bone Surg.*, 1947, 29: 560.

Combat wounds have produced many irreparable injuries to nerves of the upper extremity, as all-inclusive as the brachial plexus and as isolated as a single motor nerve to a single muscle.

Restoration of function to an individual muscle is first considered. Abduction of the index finger may be restored in case of loss of function of the first interosseus muscle, by transplanting the extensor

indicis proprius into the tendinous expansion of the first dorsal interosseus. Action of the extensor pollicis longus may be restored by transplanting the extensor indicis proprius or the extensor carpi radialis brevis (or longus) into the extensor pollicis longus. Transfer proximal to the wrist allows for normal oblique pull of the tendon around Lister's tubercle. A factor in diagnosis of function of the extensor pollicis longus is the ability to extend weakly the distal phalanx of the thumb by use of the extensor pollicis brevis. The authors prefer transfer of the extensor indicis proprius. Loss of action of the abductor pollicis longus and the extensor pollicis brevis may be corrected by transfer of the extensor carpi radialis brevis. The flexor pollicis longus is sometimes the only muscle paralyzed. Transfer of a sublimis tendon to the flexor pollicis longus is the only way to substitute a tendon of equivalent excursion. Transfer above the wrist is advised if the tendon itself is not damaged. Satisfactory function may be obtained by transferring the palmaris longus, flexor carpi radialis, wrist extensors, or the brachioradialis tendon. Occasionally, mobility of the metacarpophalangeal joint of the thumb may be limited, and then an osteotomy, bone block, or other procedure should be performed before tendon surgery is considered. In instances of loss of profundus muscle function, satisfactory repair may be obtained by suture of the dysfunctioning tendons to active tendons of the same type.

Tendinous reconstruction for permanent paralysis of the radial nerve gives good results. In cases of complete radial nerve palsy, the pronator teres insertion is divided and transplanted into the radial wrist extensors. The flexor carpi ulnaris is transplanted into the extensors of the long finger, ring finger, and little finger. The flexor carpi radialis is transplanted into the extensor pollicis longus and the extensor of the index finger. The palmaris longus is transplanted into the abductor pollicis longus and the extensor pollicis brevis. In cases of palsy of the dorsal interosseus nerve only, the same procedure is carried out with the exception of the pronator teres transfer. Occasionally, a patient may desire a more stable wrist than that afforded by tendon transplantation; this may be accomplished by wrist fusion after trial of tendon transplantation.

The ulnar nerve supplies most of the intrinsic muscles of the hand, but, unfortunately, upon regeneration after physiological interruption or surgical suture, restoration of function of the small muscles does not always occur. A wide range of disability results, from very little interference of hand function to severe clawing of the fingers and loss of adduction of the thumb. If clawing is severe enough to warrant surgery, the Bunnell type of sublimis tendon transfer to the extensor aponeurosis gives gratifying results in supple fingers. Transfers for adduction of the thumb were not performed in this series. Abduction of the index finger may be restored by transfer of the extensor indicis proprius.

Median nerve paralysis frequently results in loss of opposition of the thumb. Various procedures were utilized, especially that of subcutaneous transfer of the sublimis of the ring finger. The tendon is isolated at the wrist, severed at its insertion, and rerouted under the flexor carpi ulnaris subcutaneously, and one slip is inserted into the proximal end of the proximal phalanx and the other into the distal portion of the metacarpal.

Combined injury of the median and ulnar nerves poses a more formidable problem. Each condition must be carefully evaluated and existing functioning tendons transferred to the most important sites. In severe cases, primary arthrodesis of the wrist will allow the 3 wrist extensors to be transferred to the flexor surface for motivation of the thumb and fingers. In addition, the brachioradialis tendon may be used. In such cases, preliminary surgery may be necessary to place the thumb in optimum position. Combined median and ulnar nerve injury frequently leads to malposition of the thumb and loss of free movement due to fibrosis. Opposition of the thumb has been partially restored by using the extensor carpi ulnaris as a motor. In cases falling into the ischemic contracture group, contractures lead to gross deformity for which only a little can be done.

Brachial plexus injuries also have a wide variation of returning function. Spontaneous recovery or recovery following surgical interference must be evaluated. When maximum recovery is determined to have occurred, improvement of function can be obtained by utilizing the principles incorporated previously.

Throughout this report valuable principles are given which must be considered if maximum benefit is to be derived. Excellent diagrams and photographs illustrate the various procedures. This report portrays activity in one army general hospital and reflects work performed at other similar installations.

KENATH H. SPONSEL, M.D.

FRACTURES AND DISLOCATIONS

The Value of Patellectomy in the Treatment of Fractures of the Patella (La place de la patellectomie dans le traitement des fractures de la rotule). **Felix Lagrot and Jean Salasc.** *Mem. Acad. chir.*, Par., 1947, 73: 261.

This article is based on 4 recent, simple, transverse fractures of the patella and 1 old fracture of the patella associated with post-traumatic arthritis, all of which were treated with patellectomy. The patella was exposed by a longitudinal midline incision and removed by sharp dissection. The wound was then carefully closed layer by layer. No cast or other type of immobilization was used postoperatively. The patient was encouraged to raise his leg actively from the first postoperative day on, 5 minutes in every hour. Full extension and flexion to 90 degrees was obtained within the first month after the operation.

The increased use of this rather radical procedure was the result of observations made by many surgeons that the conservative treatment of patellar

fractures, i.e., open reduction and circular wire loop fixation had not been very satisfactory. The postoperative disability lasted for an average of 164 days. Exact apposition of the patellar fragments was rarely possible and the lack of a smoothly gliding, even, articular surface gave rise to traumatic arthritis and to permanent limitation of flexion and extension of the knee joint.

Brooke suggested that the patella was not a real sesamoid bone, since it developed independent of the tendon, but a rudimentary third bone of the leg. He found the patella to be absent in a great number of fast moving animals and concluded that it was not necessary for normal human locomotion. Although very interesting, these observations are of lesser importance in the evaluation of whether or not patellectomy is a good procedure than clinical observations of operated patients.

Schmir pointed out that patellectomy was a short procedure, of which the convalescent period was very brief (about 8 weeks) and that it did not decrease the range of motion or stability of the knee.

A more precise analysis of these 3 points showed, however, that the excision of the patella actually was a rather simple procedure, although the repair of the created defect often was difficult and time consuming. Watson-Jones recommended an overlapping "bunched" type of repair, while MacAusland used fascial strips to repair the defect, and Brooke used silk and cotton sutures. Early mobilization of the knee joint does not depend on the type of operation but rather on an intact extensor apparatus of the leg; there is, therefore, no objection to mobilizing the knee actively shortly after suture of the fractured patellar fragments. It must also be taken into consideration that the opinions as to whether or not the results of patellectomy were excellent were not alike in the literature. Bruce, Walmsley, and Cohn observed that patellectomy in dogs and rabbits eventually caused degenerative arthritis and limitation of motion in the knee joint.

Haxton proved that the patella played an important part in "the extension of the leg against resistance." Although the quadriceps of the patellectomized leg did not show any atrophy, dynamometric measurements showed a definite weakness as compared with the normal extremity. Guichard found that there was a loss of about $1/15$ of its strength. The regeneration of an imperfectly formed, smaller patellalike structure or the formation of exostoses often interfered with the normal function of a patellectomized knee. Also, in the absence of a patella the femoral condyles were entirely unprotected and subject to repeated trauma.

Excision of the patella was found of advantage in comminuted fracture of this bone, in case of a tear of the suture holding the fractured fragments together and necessitating another operation, or in cases in which a patellar osteophyte limited motion in the knee joint. Partial patellectomy was done in cases in which the absence of the excised small fragment would not disturb the articulating surface of the patella. Tavernier reported a number of good results in 1941.

The discussion of this paper was opened by SORREL. He suggested that the wire loop fixation of a simple transverse fracture of the patella was the operation of choice and stated that when it was carried out with care it showed consistently good results. In fact, Sorrel had this operation done on himself with a very satisfactory result.

BOPPE found that patients treated with wire loop fixation and who were followed up for a long period of time eventually showed complications, such as arthritis and irregularities of the patella which reduced the range of flexion in the knee joint. These patients often had to be reoperated on and a patellectomy then performed.

LERICHE had excellent results by using the method of his teacher, Vallas. After exact reduction of the patella the fragments were held together firmly by hooks which were removed after the lateral ligaments were sutured together with catgut. Motion was started after the eighth day. He thought that the absence of a foreign body (wire) favored the good end results.

ALGLAVE favored the wire loop type of repair of transverse fractures of the patella combined with reconstruction of the peripatellar fibrous structures.

MENEGAUX in his closing remarks expressed satisfaction that most of the speakers favored the conservative point of view. He agreed with Boppe that occasionally the results of the conservative procedure were not perfect. He favored excision of a small patellar fragment if it could not be held in position by a wire loop. GEORGE I. REISS, M.D.

SURGERY OF THE BLOOD AND LYMPH SYSTEMS

BLOOD VESSELS

A Study of the Results of the Surgical Treatment of Varicose Veins. Ross S. McElwee, Jr., and Bernard Maisel. *Ann. Surg.*, 1947, 126: 350.

The authors have reviewed all of the cases of varicose veins treated by operation at the New York Hospital, New York City, between 1940 and 1944. They desired to obtain information concerning the physical findings, the operation employed, the duration of hospitalization, the number of postoperative injections required to give satisfactory results, and the ultimate outcome.

As indicated by the authors, among many competent and experienced surgeons there seems to be no general agreement on the operation offering the best chance of a cure in so common a disorder as varicose veins. Follow-up studies are few and comparisons of operative procedures are rarely to be found in the current reports. The authors point out that the lack of proof that there is any one method which is superior to others in treatment of varicose veins is demonstrated by the simultaneous use of several operative procedures by the surgeons on the three services of the New York Hospital—men with the same relative ability and experience. Each service employed one of the three more common operative procedures: (1) high saphenous ligation, (2) multiple ligations, or (3) stripping the vein, without regard to the severity of the varicosities.

The operations were carried out under local anesthesia and consisted of five types of procedure: (1) high ligation of the internal saphenous vein at its junction with the femoral vein, care being taken to divide all collaterals and remove a segment of vein; (2) procedure No. 1 plus multiple interruptions by ligation and division of the vein along its course; (3) procedure No. 1 plus extirpation of a portion of the vein by means of a Mayo stripper; (4) procedure No. 1 plus retrograde injection of a sclerosing solution into the distal vein; and (5) procedure No. 1 plus excision of a prominent varix in the lower thigh or calf.

Results in 452 cases of varicose veins observed for 1 year or more after operation were recorded. High ligation of the saphenous vein combined with multiple ligations, retrograde injection, or stripping of the vein have been found to give satisfactory results in between 80 and 90 per cent of the cases. Hospitalization was longest and the degree of discomfort was greatest following retrograde injection or stripping, and was least following high ligation or multiple ligations.

Complications were more frequent after multiple ligation though the majority were not serious. Phlebitis occurred more often after retrograde injection. There were no proved cases of pulmonary embolism, and no deaths. High saphenous ligation plus retrograde injection required the smallest number of postoperative sclerosing solution injections to attain satisfactory results.

The authors conclude that multiple ligation (including, of course, high ligation of the saphenous vein) is the operation of choice.

EDWARD F. LEWISON, M.D.

The Effects on Venous Endothelium of Alterations in Blood Flow Through the Vessels in Vein Walls, and the Possible Relation to Thrombosis. James F. O'Neill. *Ann. Surg.*, 1947, 126: 270.

At the suggestion of Cecil K. Drinker, the author undertook the study of spontaneous thrombophlebitis, or phlebothrombosis, by observing the nutrition of vein walls in specially prepared flat histologic preparations.

Relevant to the etiology of the clinical menace of venous thrombosis, the author presupposes that an imbalance between any two of the following factors must exist. These factors are: (a) alteration in the quality or quantity of blood constituents; (b) alterations in the rate of flow of blood in the veins; and (c) alterations in the endothelial coats of the veins. This paper is devoted principally to a consideration of the last named factor, the vein walls, and some of their physiologic relationships.

Venous thrombosis can be produced experimentally by damaging the vein walls in many various ways. This hardly resembles any known pathologic process which may occur in postoperative or postpartum patients, or in individuals afflicted with systemic infections, cardiovascular disease, or in other debilitating disorders wherein venous thrombosis may occur.

Since few investigators have studied the vascular supply to vein walls, the author was virtually a pioneer in developing a most ingenious technique for the histologic preparation of flat vein wall segments. Preparations so made allow for careful examination of the vasa venarum and a more exact anatomic description of blood vessel patterns in vein walls. Dilute silver nitrate solution is used in staining and studying the inner coats of the vein walls, and a benzidine stain is used for outlining the vascular plexus in the vein walls.

Carefully devised experiments were performed to study the effect on the vein walls, principally on the endothelium, when the blood supply via the vasa venarum was cut off. Conclusions indicated that division of all blood vessels, lymphatics, and nerves to a given vein segment, over a period exceeding 4 to 6 hours, resulted in increasing degrees of endothelial desquamation. Intravascular clotting, however, seldom occurred without the presence of stasis, or at least partial obstruction to normal blood flow.

EDWARD F. LEWISON, M.D.

The Chronic (Second) Stage of Thrombosis in the Lower Extremities. Inge Birger. *Acta chir. scand.*, 1947, 95: Supp. 129.

The author divides thrombosis of the lower extremities into phases: the acute or primary stage, and the chronic or secondary stage. The chronic phase is defined as the venous insufficiency which remains after stage 1. Slowing of the blood flow, alterations in blood composition, and, to a lesser extent, intimal damage, are presented as the causes of thrombosis, which is said to originate in the foot and lower leg in the vast majority of cases. A brief review of earlier and contemporary opinions concerning the etiology and development of thrombosis is presented and the dominant role of deep thrombosis in the etiology of leg ulcers is stressed.

The author's personal investigation was based upon a study of 3,005 patients with peripheral vascular disease in the lower extremities. Often the patients were quite free from any symptoms up until the time that edema, induration, eczema, and ulceration arose fairly acutely after a lapse of several years. The combination of edema and sclerosis causes the leg to assume a typical "bobbin shaped" appearance. Women seemed especially susceptible to the development of thrombosis. Whether a secondary chronic stage will develop depends upon whether a condition of venous insufficiency is present or will develop in time.

Pathologically, the thrombosis within the vein provokes a reactive process which causes it to adhere to the walls and also causes lymph blockage and vasospasm; this gives rise to the typical "white leg." In the late stage, an obstructive inflammatory thrombosis usually develops, with destruction of function of the involved valves. In the chronic stage of thrombosis, the fundamental causes of the degenerative (and in some measure proliferative) changes which take place in the tissues of the lower leg, especially in the form of induration, eczema, ulceration, and sometimes elephantiasis of the skin, are venous stasis and the chronic edema in the lower leg which arises therefrom.

Two-thirds of the patients had permanent swelling of the leg since the acute thrombotic stage; a follow up study of 58 patients revealed that after a lapse of at least 16 years following acute thrombosis of the lower extremities, one-fourth were completely asymptomatic, while three-fourths were suffering from chronic venous insufficiency.

Concerning the relationship of trauma to lower extremity thrombosis, there is a striking frequency of thrombosis following femoral neck fractures, a low frequency in femoral shaft fractures, and a predominant frequency in all injuries below the knee. It is not necessary for the responsible injuries to be severe, as even contusions of the lower leg can cause thrombosis to develop. The thrombotic process usually develops in the injured leg, but it can occur on the opposite side.

The prophylactic treatment of venous thrombosis consists of exercise, early ambulation, and the use of anticoagulants. As soon as the presence of thrombosis is diagnosed, it is of the utmost importance to prevent further thrombosis so as to avoid a fatal embolus and to maintain a patent popliteal vein, which is so important in preventing invalidity in the secondary stage. Heparin and dicumarol are used to "abort" the thrombotic process; femoral or iliac vein ligation is thought to encourage, rather than prevent, the chronic stage of venous insufficiency. If one cannot succeed in freeing the thrombosed leg from edema during an adequately long period of convalescence by the use of suitable measures (including massage, gymnastic treatment, and sufficiently powerful compressive bandage), then the patient has passed into the chronic stage of thrombosis. Treatment for this chronic stage consists of a bandage which is firm and elastic, without grooving or strangulating the leg, or impeding the perspiration. The technique of applying Jaeger's elastic bandage is presented, together with prescriptions of ointments and solutions for local ulcer treatment. In the author's opinion, there is no great need to operate (vein ligation or injection) because, as a rule, one can manage with the conservative compression treatment. All patients were treated while fully ambulatory and the great majority have been able to continue their daily work while under treatment. It appears that the primary results of this treatment are good, but only 16 per cent of the patients have been observed to be still fit after the lapse of a year or more. There is, however, reason to believe that many of the patients who did not return were cured or at least remained free from trouble for more than a year. ROBERT A. NABATOFF, M.D.

Congenital Arteriovenous Fistula between the Internal Maxillary Artery and the Pterygoid Plexus. Frank Gerbode and Emile Holman. *Surgery*, 1937, 22: 209.

Observations by Sabin and Woolard indicate that congenital arteriovenous fistulas are due to a persistence of embryonic vascular channels. Arteries and veins arise from a common capillary plexus, affording an explanation for the occurrence of abnormal communications. Congenital arteriovenous fistulas exhibit the same circulatory phenomena produced by traumatic fistulas, if the size of the communication is large. The bradycardiac phenomenon on closure of the fistula is not demonstrable when numerous communications exist, precluding complete occlusion of all the fistulas. Cardiac enlargement occurs if the communications are large, and, after obliteration of the fistula, the heart size has been observed to return to normal. This effect was not described by Dandy in cerebral arteriovenous fistulas, and it has not been seen in many of the cirsoid types with multiple small openings between the arteries and veins. The increased vascularity of the tissues near an arteriovenous fistula causes stimulation of the growth of long bones and increased surface temperature.

In the surgery of congenital arteriovenous fistulas of the face and neck, as is to be expected, cure is un-

certain unless the actual communications are either ligated, extirpated, or thrombosed. Of the 23 patients whose cases were reported in the literature and who were treated surgically, only 13 were cured. In 6 instances a direct attack on the involved vessels with excision was successful. Four patients were cured by ligation and division of multiple small fistulas. Only 1 of the cures was effected by ligation of the principal artery leading toward the involved vessels. Reid and McGuire reported a cure of congenital fistula between the external carotid artery and the external jugular vein, in which case the artery and vein were ligated and transected, the proximal vein then being twisted to occlude the fistula. Ferris Smith reported the cure of an aneurysm in the tympanum, in which he ligated the veins and packed the aneurysm.

In 12 of the cases reported in the literature the patient required more than 1 operation to relieve the symptoms partially or totally. In the case presented, considerable improvement resulted after 1 operation. The patient was a 6 year old girl who had noted a buzzing in her left ear as long as she could remember. There was a swelling below the ear, and a pronounced thrill could be felt over the involved area. The murmur could be diminished by pressure over the left common carotid artery, but pressure over both common carotid arteries was required to obliterate it. X-rays revealed the left half of the mandible to be larger than the right. Angiography with 15 c.c. of thorotrast injected into the left common carotid artery revealed that the opaque medium went directly into the external artery, avoiding the internal carotid, and then into the internal maxillary artery. Here, abnormal arteriovenous communications between the latter artery and the veins of the pterygoid plexus could be seen. Since direct attack on the fistula would have involved a bloody and disfiguring procedure, and since compression of both common carotid arteries had been necessary to stop the murmur, which indicated that some blood supply to the fistula was coming from the opposite side, it was decided to pack the artery with muscle at the site of the fistula and thus directly occlude the abnormal communications.

At operation a very large, pulsating external jugular vein was ligated and transected; then the branches of the external carotid artery proximal to the fistula were ligated, and a 5 cm. by 3 mm. strip of sternomastoid muscle was inserted into the external carotid so as to extend into the area of the fistula. The postoperative course was uneventful and the patient was discharged on the eighth postoperative day. Two and a half months after operation, a faint bruit could be heard just in front of the left ear and pressure over the right external carotid artery stopped this murmur, which indicated that this vessel was now supplying a small opening not occluded by the muscle. The size of the heart has diminished appreciably since operation. The preoperative blood pressure was 115/60; 1 month after operation it was 124/80. The patient was no longer conscious of the murmur.

A summary of the cases of congenital arteriovenous fistulas of the face and neck reported in the literature is then presented. ROBERT A. NABATOFF, M.D.

Fatality following the Use of Intravenous Ether in the Treatment of Peripheral Vascular Disease. Sydney Sewall. *Bull. Hosp. Joint Dis.*, N. Y., 1947, 8: 33.

The author presents a case in which death followed the use of ether intravenously in the treatment of peripheral vascular disease. Postmortem examination revealed numerous pulmonary fat emboli and parenchymatous degeneration of the liver and kidneys. A search of the literature showed that ether was found not to be as harmless as previously believed. In view of the findings, the author suggests that cases be well selected before treatment by intravenous injection of ether is undertaken; that liver and renal functions be carefully determined before treatment; that these tests be carried out at frequent intervals during the period of treatment; and that treatment be immediately discontinued if any impairment of the function of these vital organs is found.

A history of the chemical production of ether is presented. The introduction of its use in medicine, and its use for therapeutic purposes is described.

Ether was first used intravenously in the treatment of peripheral vascular disease in 1945. Prior to its use intravenously it was used intramuscularly, but the objection to this method was that ulcers developed at the site of injection. The mechanism of its action is thought to be due to the increased flow of blood in the peripheral vessels caused by the action of ether gas on the small peripheral collaterals. In the treatment of peripheral vascular disease, a 2½ per cent solution in 1,000 c.c. of sixth molar lactate, saline, or glucose is given daily for 12 consecutive days. After a rest period of 2 days, 12 more daily injections are given.

The author presents a case in which ether was used in the manner described. The patient was a 75 year old negro female who had an obliterating arteriosclerosis of both lower extremities. Amputation of a fifth toe, because of gangrene, was followed by ulceration at the site of amputation. A 2½ per cent solution of ether and dextrose was given intravenously for 12 days. After a 2 day rest period, treatments were again resumed. With this treatment, the patient improved generally and locally. She experienced a sense of warmth in both lower extremities and a feeling of well being. Healthy granulation tissue began to appear in the wound. On the third day of the second course, the patient developed a shaking chill followed by an elevated temperature. The treatment was stopped and on the morning of the second day after cessation of treatments the patient died. On postmortem examination, the liver was found to be extremely friable, and practically crumbled when handled. Microscopic examination revealed a severe parenchymatous degeneration. The probable cause of death was revealed in the lung fields which contained numerous fat emboli throughout.

The author presents a brief review of the toxic effects of ether. He notes that Mann (5) in 1926 showed that ether produced demonstrable effects on hepatic activity. The capacity of the liver to store glycogen is also disturbed by ether. The liver, under ordinary circumstances, converts lactic acid to glycogen, but during ether anesthesia it does not seem able to do this and the liver glycogen is depleted.

HERBERT F. THURSTON, M.D.

Functional Survival of Autogenous and Homogenous Transplants of Blood Vessels. An Experimental Study. Carl S. Williamson and Frank C. Mann. *Arch. Surg.*, 1947, 54: 529.

A series of 6 medium sized dogs were selected at random. This group of animals was divided into 3 pairs so that both animals in each pair would act both as a donor and as a recipient. With the animals under ether anesthesia and with the use of aseptic technique, sections from the carotid artery and the jugular vein of each animal were removed and exchanged for similar sections removed from the same vessels of the other member of the pair.

Of the 12 transplantations (6 venous transplants and 6 arterial transplants) 10 resulted in nonfunction after an elapsed time of 56 to 62 days. In arterial transplant, function could be observed grossly at the time of removal, and in the other, function could not be determined grossly but a limited degree of function was observed upon histological examination. All the venous transplants had ceased to function at the time of removal, and the remaining arterial transplants had also ceased to function. The results in 1 of the animals was compromised by a severe postoperative infection. Grossly, there was nothing to account for the failure of the vascular transplants to survive. The histologic picture in both the arteries and the veins varied widely but was consistent in some respects in all the experiments.

The most common histologic feature in all thrombi in both arteries and veins was the tendency toward vascularization in the thrombi, which occluded the lumens of the vessels. This vascularization included the walls of the vessels themselves. These newly formed blood vessels were fairly large in some instances and were evidently serving as conduits for a considerable amount of blood in both the arterial and the venous transplants. The thrombi which were present in the arterial transplants had a spongy appearance in some instances, but those in the veins were more solidly organized and there was a decided tendency for the clot to be divided into segments by fibrous septums.

The destructive process in the arteries was less severe than in the veins, and there was also a greater tendency toward canalization of the thrombi. In general the intima of the arteries was fairly well preserved, but in a few instances it had been largely destroyed and replaced by fibrous tissue. The muscle fibers of the media were also fairly normal in number and arrangement, but in some of the vessels in which the reaction had been severest many of the muscle fibers and much of the elastic tissue had been replaced by fibrous tissue. In summary, it can be said that the structure of the arterial walls of the transplanted segments of vessels had not been severely damaged except in a few instances.

Uniformly, the destructive process in the sections of the transplanted veins was complete. All the veins were thrombosed, and, while there was a tendency toward vascularization of the thrombi, this process was not pronounced. The thrombi were more solidly organized and seemed to be more firmly attached to the walls of the veins than they were in the arterial transplants. The venous walls themselves were for the most part poorly preserved. There was extensive replacement of the normal mural structures with fibrous tissue, and in some regions this replacement was almost complete. An explanation of the severity of the reaction in the veins is not obvious. In all the transplants, both arterial and venous, there was a tendency toward vascularization of the walls of the vessels, as well as of the thrombi which occluded the lumens. This characteristic was most pronounced in the arterial transplants. In some instances this development had progressed enough to be considered important as a channel for the arterial circulation. The status of these vessels in relation to the ultimate survival of the transplants remains a problem for future investigation.

The authors emphasize the following points:

1. The technique of vascular surgery is well established, and the surgeon who is willing to accept the requirements necessary for success in this work can expect satisfactory end-results in the main.

2. The autogenous transplantation of both arteries and veins is a feasible surgical procedure in the light of present knowledge.

3. Homogenous transplantation of blood vessels, as well as of other body structures, is not justified in the light of present knowledge.

4. There is a striking tendency for capillaries to develop in both the thrombus and the wall of the vessel in homogenous vascular transplants. This tendency is most conspicuous in the arterial transplants.

BLOOD; TRANSFUSION

Hemolytic Intragroup Transfusion Reaction Due to a Hemagglutinogen not Hitherto Described (Reaction transfusionnelle hémolytique intra-groupe due à un hémagglutinogène jusqu'ici non décrit). **Alexandre S. Wiener and Eve B. Sonn Gordon.** *Rev. hemat.*, 1947, 2: 3.

Although 90 per cent of hemolytic reactions may be avoided by testing for the Rh factor, when the patient is Rh positive it is often difficult to determine whether a chill following a blood transfusion is specific and hemolytic, or nonhemolytic due to pyrogens or to other nonspecific agents. In these atypical reactions the hemolysis is of gradual onset so that urinary suppression is not a usual consequence. Nevertheless, after hemolytic reactions the red blood count is not increased and it may even drop. Consequently, a diagnosis of hemolysis may be made by determin-

ing if the red corpuscles of the donor have been destroyed or are still present in the recipient's blood. The authors call this "differential agglutination."

A case is described in which violent hemolytic reactions occurred after a series of transfusions. These reactions were explained by the presence in the patient's serum of an abnormal univalent isoantibody unrelated to groups A, B, O, types M, N or types Rh or Hr.

The blood factor has been given the provisional designation of Si. The agglutinogen has been found in the blood of 19 of 148 Caucasians tested and it seems to be inherited as a simple dominant mendelian factor. THEODORE B. MASSELL, M.D.

Peritoneal Irrigation for Acute Renal Damage following Incompatible Blood Transfusion: A Discussion Based on 3 Cases. E. E. Muirhead, A. B. Small, A. E. Haley, and J. M. Hill. *J. Lab. Clin. M.*, 1947, 32: 988.

The authors stated that peritoneal irrigation used for the treatment of patients suffering from renal insufficiency following incompatible blood transfusion clears substantial quantities of urea and presumably other waste products from the body. However, they believe that the use of crystalloid solution for irrigation appears to be related to 2 major complications, namely, the accentuation of acidosis and the absorption of water and salts from the peritoneum. These complications are considered to be deleterious to the progress of these patients during the phase of renal insufficiency, and they may retard the onset of diuresis. Muirhead, Small, Haley, and Hill have suggested a "three-phase" regime which seems to oppose these complications. They divided the clinical course of patients experiencing incompatible blood transfusions into: (1) hemolysis and hypotension, which are characterized by a sudden onset with apprehension, tightness in the chest, backache, dyspnea, cyanosis, and mental confusion, hypotension, chills and fever, and hemoglobinemia-hemoglobinuria; (2) renal insufficiency which is attended by oliguria, blood casts in the urine, hypertension, azotemia, altered chemical pattern of blood (mainly depressed serum sodium, calcium, blood chloride concentration, and carbon dioxide combining power of plasma), and mounting antibody titer; and (3) copious diuresis which is accompanied by marked water salt loss from the body. Each phase requires its own distinctive type of management.

During the first phase, blood transfusion of undoubted compatibility should be given to cope with anemia and lowered blood volume, thus decreasing the period of hypotension.

During the second phase, forcing fluids appears deleterious because the kidneys are not in a position to handle water and salts. The best results during this period have been obtained by restricting the fluid intake to a conservative estimated insensible loss plus the scanty urinary output (a total usually of from 800 to 1,500 ml. daily for from 6 to 8 days). A high caloric, low salt formula is given with this fluid, plus water soluble vitamins. Sodium bicarbonate in doses of from 4 to 6 gm. is given daily to cope with an excessive lowering of the carbon dioxide combining power of the plasma. This regime is based on the premise that damaged kidneys require time for healing. When the diuresis appears the water salt loss through this means is replaced. Such losses may require from 20 to 40 gm. of salts daily plus from 5,000 to 10,000 ml. of water. As soon as possible the patient is allowed to adjust his own intake and output.

It has been the experience of the authors that when patients are overloaded with water and salt they die, or the onset of diuresis is delayed.

ROBERT TURELL, M.D.

SURGICAL TECHNIQUE

ANTISEPTIC SURGERY; TREATMENT OF WOUNDS AND INFECTIONS

Bone Abscess from Human Bite. A. T. Andreasen. *Brit. J. Surg.*, 1947, 34: 411.

The author reports a case of bone abscess arising from a human bite; it is the only case in the literature.

A 21 year old army officer was bitten at the base of the right index finger by an enemy soldier. The bone was exposed and the soft parts were badly torn. The wound became badly infected but healed in 2 weeks with good return of function. However, the patient was troubled with a slightly tender, painful swelling over the palmar aspect of the metacarpal head.

Several weeks later the wound area began to swell and became increasingly painful. It became red and glossy. There was considerable edema of the dorsum of the hand. An abscess and marked tenderness over the metacarpal head appeared. After drainage, the wound rapidly healed. The organisms were hemolytic staphylococci and fusiform bacilli of the type seen in Vincent's angina.

Some weeks later a diffuse swelling of the same region appeared, and the patient complained of aching. No fluctuation was noted. On x-ray examination 2 clear areas of abscess with considerable periosteal reaction about them were seen in the head of the second metacarpal. The hand was immobilized in plaster for 2 months to allow the swelling to subside.

After preoperative sulfonamide and brachial plexus block anesthesia, an incision was made along the radial border of the dorsal aspect of the second metacarpal from 1 cm. above the metacarpophalangeal joint to 1 cm. proximal to the base of the bone. The superficial fascia was incised in the line of the incision. The incision through the deep fascia was so placed as to leave the compartment containing the tendons intact. The incision was then carried down to bone through the periosteum near the radial edge of the dorsum of the metacarpal. The periosteum was elevated. With a fine mastoid gauge, the lower abscess was opened. After a check was made with a roentgenograph, the upper abscess was opened, care being taken not to open into the joint. The periosteal flap was replaced over the bone, the skin loosely sutured, and the hand placed in a loose posterior plaster cast holding the index finger in flexion at the metacarpophalangeal joint. The wound healed per primam and there was only slight residual limitation of flexion. The bone abscess showed the same bacteria as the soft tissue abscess.

Apparently the original deep lesion involved the periosteum and bone and there was local abscess formation which was only partially evacuated through the fascia and skin. As the unevacuated abscess spread through the periosteum, it was eventually trapped by the new bone formed.

The author recommends the described incision for use in approaching the second metacarpal. It gives good access and does not disturb the fascial space around the extensor tendons. He points out that the superficial fascia often may consist of 2 layers. Recognition of this is important to avoid unnecessary stripping up of the wrong fascial layer.

An arrangement is described by which x-rays can be taken during the operative procedures on the hand and forearm. It is of value in avoiding injury to a joint space.

The author uses a wooden bowl beneath the palmar surface of the hand during surgery to steady the hand.

Meticulous asepsis is well worth the additional care required.

Rehabilitation has been largely responsible for the better functional results following the treatment of hand injuries and infections.

ROBERT R. BIGELOW, M.D.

Caronamide and Penicillin. J. William Crosson, William P. Boger, Cristopher C. Shaw, and A. Kathrine Miller. *J. Am. M. Ass.*, 1947, 134: 1528.

The authors studied a new drug, caronamide (4′-carboxyphenylmethanesulfonanilide), which when administered by mouth to patients receiving penicillin produces a physiologic and reversible inhibition of the excretion of this antibiotic resulting in elevation of the concentration of penicillin in the plasma. With the aid of caronamide, it is now possible to sustain a high plasma concentration of penicillin in the treatment of resistant infections.

Normally, about 80 per cent of penicillin in the urine is excreted by the renal tubules and the remaining 20 per cent by glomerular filtration. It has been known that iodopyrin and para-aminohippuric acid which are excreted by the renal tubules can inhibit the excretion of a third substance—penicillin. These drugs act on a "mass action" basis to saturate functionally the transport mechanism of the renal tubules and thus inhibit the elimination of penicillin. Caronamide, on the basis of clinical trial, has been found to be capable also of producing a reversible inhibition of penicillin by the renal tubules. The effectiveness of this drug depends on a "substrate competition between penicillin, which is excreted by the tubules, and 4′-carboxyphenylmethanesulfonanilide, which is essentially refractory to excretion by that transport mechanism."

In this investigation each patient was studied while receiving the drug as well as in the preliminary control period and in the postdrug control period; he thus served as his own control. A group of 6 patients given penicillin orally (100,000 units every 4 hours) and caronamide orally (2 gm. every 4 hours) showed increases of penicillin blood levels of from 2

to 7 times those observed during the control periods. Buffering agents were not administered with the penicillin, the patients were allowed to take fluids freely, meals were given in accordance with hospital routine, and no effort was made to enhance the penicillin levels apart from the administration of caronamide.

Another group of 8 patients were given penicillin intramuscularly and caronamide orally in varying dosages. Five of these patients given either 1.5 gm. of caronamide every 3 hours or 2 gm. every 4 hours showed an increase of the penicillin plasma levels of from 2 to 7 times those observed during the control periods. Three patients given only 1 gm. of caronamide every 2 hours failed to show the same degree of increase of penicillin concentrations.

Six patients receiving penicillin in beeswax and oil (Romansky formula) and oral caronamide also showed an increase in penicillin plasma concentrations, while 3 other patients yielded equivocal results. This phase of the investigation has thus far been incompletely studied.

This clinical investigation suggests that from twofold to sevenfold increase of penicillin plasma concentration may be expected if about 2 gm. of caronamide are administered concomitantly with penicillin (given orally or parenterally) every 3 and 4 hours, respectively. Thus far no systemic toxicity was noted in the patients who received caronamide. This drug promises great therapeutic usefulness in the treatment of lesions which require high penicillin concentrations. ROBERT TURELL, M.D.

Anuria Observed in Connection with Penicillin Therapy. Bengt Nylén. *Acta chir. scand.*, 1947, 95: 483.

Reports in the literature on toxic reactions in penicillin therapy, with special regard to the kidneys, are reviewed, and the author presents a case of anuria which probably resulted from toxic effects of penicillin on the kidneys. In an experimental investigation on rats he found that the penicillin used had no diuresis inhibiting effect on animals with damaged kidneys.

Minor transient rises of the nonprotein nitrogen have been reported in penicillin therapy but albuminuria or other signs of renal damage were lacking. It has been found that penicillin is excreted for the most part through the tubules. When renal function is impaired, penicillin is excreted more slowly and to a lesser extent, and the penicillin level in the blood is higher than in normal cases. Anuria has been reported in a case of acute meningitis treated with sulfamerazine and penicillin, and has been produced experimentally in rabbits by the injection of large doses of penicillin. The reactions observed in penicillin therapy are generally attributed to impurities in the penicillin.

In order to determine whether penicillin, in the case of damaged kidneys, has any effect on diuresis, the following experiment was performed. The left kidney was removed from a group of male rats and 2 weeks later the upper and lower poles of the right kidney were removed. Control animals were killed immediately after the second operation and the remainder of the kidneys was removed and weighed for comparison with the amount of renal substance in the experimental animals. After about 1 month the experimental animals were placed in cages where the urine could be collected, measured, and tested for albumin daily. Water intake and weight were also recorded. These animals were then divided into two groups, one group of which received daily intramuscular injections of penicillin in 6 divided doses for 4 days. Six days later the animals were killed and the kidneys were weighed and prepared for histologic examination. Urea nitrogen determinations were made before, during, and after the test.

In these tests the experimental animals showed no difference from the controls in regard to the amount of urine after the injection of penicillin for 4 days, nor was there any observable difference between the experimental animals and controls with regard to weight, albumin reaction, urea nitrogen, and histologic examination. According to this experiment it seems that penicillin injection in rats whose kidneys have been damaged causes no inhibitory effect on diuresis. The purity of the penicillin used in the experiments was about 1,300 Oxford units per mgm.; this penicillin was considerably purer than the penicillin used in the clinical case. The purity of the penicillin may account for the negative result in the experimental test. JOHN L. LINDQUIST, M.D.

ANESTHESIA

Spinal Fluid Findings in Spinal Anesthesia. M. Gene Black. *Anesthesiology*, 1947, 8: 382.

A study of the spinal fluid in 200 patients was made to determine the effect of spinal anesthesia. The controls consisted of 75 patients who had no previous record of spinal anesthesia. The spinal fluids taken preoperatively were within normal limits. In 60 cases in which the fluid was taken from 30 days to 10 years after the spinal anesthesia, there was, in comparison, a mild increase in protein, chiefly because the interval was less than 3 months in 20 cases. In 25 cases, specimens of spinal fluid obtained before and after continuous spinal anesthesia were examined. Protein variations were negligible, which suggests that the time interval was inadequate for meningeal or tissue irritation to be demonstrated. The spinal fluid sugar in this group presents a marked rise at the end of operation when the patient was kept in the horizontal position.

Pontocaine and glucose were the agents used in this study. It is thought probable that the rise in spinal fluid sugar was caused by pooling of the glucose at the site of injection. The Trendelenburg position promotes diffusion and it is believed that diffused glucose promotes the metabolism of the central nervous system.

It is suggested that pontocaine or any similar anesthetic agent used intraspinally may produce

transient irritation, the possible exception occurring in the rare individual who is allergic to the drug. Glucose, when used in conjunction with spinal anesthetic agents and if permitted to diffuse by use of the Trendelenburg position, may be helpful rather than harmful to the tissues of the central nervous system.

MARY FRANCES POE, M.D.

Discussion on Further Experiences with Curare. Frederick Prescott, Geoffrey Organe, Barnett Mallinson, John Gillies, and Others. *Proc. R. Soc. M.*, Lond., 1947, 40: 593.

FREDERICK PRESCOTT gives some aspects of the clinical pharmacology of curare. Curare in its crude state is totally unfit for clinical use. Clinically, the only alkaloid preparation of interest is d-tubocurarine chloride. In clinical doses this drug has no action other than that of paralyzing skeletal muscle by blocking conduction at the myoneural junction.

D-tubocurarine chloride belongs to the quaternary ammonium salt compounds. In man, the muscles are affected after curarization in the order of their phylogeny; i.e., muscles supplied by the cranial nerves first, then those of the limbs, back, abdomen, intercostal region, and, finally, those of the diaphragm.

Ephedrine is said to potentiate the action of prostigmine, which is the antagonist of curarizing drugs. This effect has not been confirmed in man. It is necessary to give atropine when prostigmine is used to prevent the stimulation of curarization on the parasympathetic nervous system.

Curarelike drugs form a block at the myoneural junction, possibly by combining with the receptor substance in the muscle. They do not interfere with the production of acetylcholine.

Experimentally, the view is now held that curariform drugs act anywhere in the nervous or muscular systems where acetylcholine is the chemical mediator.

The curariform action of ether was noted as far back as 1914. Pentothal in high blood concentrations has the same effect.

The experimental work of Smith *et al.* shows that d-tubocurarine has no significant central stimulant, depressant, or analgesic action in man. Cole found that the total nonanoxic dose of intocostrin in dogs was 23.3 units per pound. In man intocostrin and d-tubocurarine appear to have no effect on the cardiovascular system in clinical doses.

Comroe and Dripps describe the formation of histaminelike wheals after the intracutaneous injection of curarizing drugs. The author believes that there is danger of bronchospasm in man if the patient is lightly anesthetized or conscious and if the dose of the curarizing drug is small.

Gross and Cullen believe that d-tubocurarine causes relaxation of the smooth muscle of the small intestine, but often the gut appears to be contracted. It is difficult to separate the effect of the drug from that due to the drugs used for premedication and anesthesia.

The fact that both d-tubocurarine and intocostrin are rapidly metabolized and eliminated suggests that slow administration by an intravenous drip is unsatisfactory, and this fact has been confirmed by use on a volunteer.

Both of these drugs produce salivation. For this reason patients should be atropinized before receiving d-tubocurarine or intocostrin.

GEOFFREY ORGANE describes further experiences with d-tubocurarine. Case records were selected to show that the results of using d-tubocurarine in anesthesia are not always all that could be desired. The author and Prescott did the first experimental work on the preparation known as tubarine, and Organe believes that, although its use should be continued, their early clinical reports were colored with "roseate enthusiasm." Among the 86 patients who underwent abdominal operations there were 24 with major and 15 with minor chest complications. All anesthetic agents and techniques were involved in this list of complications. One patient died of bronchopneumonia, 1 of the original disease, and 1 was later found to have bronchiectasis. The others appeared to be recovered at the time of their discharge, which was not delayed in any case.

Tubarine has been valuable in the relief of laryngospasm, but does not always prevent it. Case reports are presented.

Organe believes that tubarine is a valuable aid in bronchoscopy and esophagoscopy, while with pentothal alone they are dangerous procedures because of the difficulty of maintaining a clear airway. When tubarine is added the airway remains clear and the patient breathes quietly. Venespasm is a common accompaniment of severe blood pressure fall with most anesthetic agents, but is much less common when tubarine is used. This author ends his discussion by emphasizing that one must neglect none of the usual precautions in using tubarine.

BARNETT MALLINON gives some general aspects of the technique of curarization. One of the most significant aspects of the advent of curarization is that it can reduce the number of spinal anesthetics administered. Curare can be given in second plane anesthesia or sometimes in the first plane; with myanesin first plane anesthesia is usually adequate. If anesthesia can be of a lighter plane there is less damage likely to be inflicted on the patient.

This author has found the use of curare and pentothal for laryngeal intubation disappointing. Curare and pentothal facilitate intubation, but the dose must be unusually large. Large doses are to be condemned under any circumstances.

A. C. FORRESTER. Curare was used in a series of patients in shock for nonabdominal surgery. This author believes that curare protects against shock, but if the curarization is allowed to wear off while the anesthetic is still very light, a condition resembling shock is produced. In this situation the patient's general condition will improve if more curare is given.

JOHN GILLIES. This discussant presented the case report of an 8 weeks old infant on whom curare was used. He appealed to anesthetists using curare to study carefully all the published experimental work.

JOHN HALTON. People who use curare must learn that it is not enough that the patient is just breathing. The respiration must be "aided" from the moment of the injection until the curare effect has passed off.

L. C. MOUNTFORD expresses the opinion that the larynx and trachea should be cocainized prior to the use of either curare or pentothal for intubating the trachea.

H. B. WILSON discussed a series of cases in which myanesin was used.

MASSEY DAWKINS. In a series of 300 patients anesthetized with curare the mortality rate was about 12 times greater than that following the use of chloroform.

CECIL GRAY. The 2 main dangers of tubocurarine appear to be its use by the inexperienced, and the occurrence of regurgitation of the stomach contents. There is an insidious "flowback" of the stomach contents due to the abdominal relaxation of the esophageal muscle and sphincter. EDITH EASON, M.D.

Resuscitation of the Heart in Anesthetic Syncopes (A propos de la ranimation du coeur dans les syncopes anesthésiques). **E. Desmarest, J. Lhermitte, and G. Jacquot.** *Anesthésie*, Par., 1939, 5: 481.

The authors discuss in great detail a case of anesthetic syncope which occurred at the final stage of a hysterectomy performed under nitrous oxide anesthesia. After artificial respiration and the intracardial injection of adrenalin had been unsuccessful, the surgeon severed the sutures of the abdominal wall and performed massage of the heart from the abdominal cavity through the diaphragm. Five minutes after the beginning of the massage, the heart started contracting again, and a little later spontaneous respiration set in. Only much later the pupils, which had been in maximal dilatation, came back to normal. The patient died 64 hours after the accident without having regained consciousness. During these 2½ days, the patient developed signs of severe cerebral irritation: general tetanic convulsions which occurred every 30 to 40 minutes, hyperpyrexia, the positive Babinski sign, and hypertension of 200 mm.

The histologic examination of the brain revealed extreme damage caused by anoxia during the arrest of the circulation. The foremost finding was widespread lipoid degeneration. This degeneration involved practically every cell of the cerebral cortex, also the endothelium of the blood vessels in this region; and the adventitia of the precapillaries showed numerous lipoid droplets. In the striate body and in the cerebellum the lipoid degeneration was less marked, whereas the white matter and the gray cells of the medulla did not show any trace of lipoid degeneration.

Slides stained according to Nissl revealed caryolysis in the pyramidal cells, hyaline degeneration, fibrillolysis, chromolysis, and other degenerative signs which are described in great detail. The neuroglia, especially in the frontal lobe, presented signs of proliferation and hyperplasia.

A review of the literature shows that about 100 cases are on record in which massage of the heart was done in anesthesia accidents; in 25 it was successful. Several of these cases showed the same course as the present case: survival for 2 or 3 days after the successful massage of the heart, and death under the signs of severe brain damage. On the other hand, there were cases reported in which heart action and respiration had stopped for as much as 15 minutes before heart massage was successful, without leaving any signs whatever of brain damage.

The authors attach special prognostic importance to the condition of the pupils. They believe that total mydriasis of longer duration is a sign of damage done to the ciliospinal center which gives a poor prognosis even when the circulation and respiration have been restored. WERNER M. SOLMITZ, M.D.

PHYSICOCHEMICAL METHODS IN SURGERY

ROENTGENOLOGY

Radiologic Survey of the Salivary Glands (Estudio radiologico de las glandulas salivares). **Raúl Leborgne.** *Bol. Soc. cir. Uruguay*, 1947, 18: 55.

The radiographic survey of the salivary glands is done with plain roentgenograms by sialography, the latter with the injection of an opaque medium.

Plain roentgenograms are used for visualization of stones and, as these are small and not very opaque, it is necessary to use soft rays and appropriate views. Occlusal roentgenograms are used for visualization of the anterior three-fourths of Wharton's duct, and lateral roentgenograms for demonstration of the hemimaxilla of either side and to complete the examination of the duct and its gland.

The anterior end of Stenson's duct is viewed with an intraoral roentgenogram of the cheek, and the parotid gland with lateral and posteroanterior roentgenograms of the region.

For the parotid gland the sialography apparatus consists of a syringe of 2 c.c.; 1 blunt end needle 5 cm. in length with a 2 mm. gauge and a conic dilatation of 2 mm. near the distal end, which is used as a stopper of the salivary duct and to avoid the reflux of the injected liquid; and a dilator. For the submaxillary gland a curved needle with a 0.51 mm. gauge is required. Iodinol is the dye used; it is an iodate oil of 40 per cent strength.

The injection of the parotid gland is made with the patient in the supine position. The small papilla with the orifice of Stenson's duct is located on the oral mucosa in front of the second premolar. This is explored with the dilator, then it is injected with 1 c.c. of dye until the patient feels a slight annoyance in the parotid region. Then, a lateral roentgenogram is taken, if possible, a stereoscopic view, and the posteroanterior view. For the submaxillary gland the same technique is used, the injection being made by way of Wharton's duct on the floor of the mouth. The oil is eliminated soon after the examination. The radiographic factors are 3½ seconds, 15 m.a., 40 cm. focal irradiation distance. The Bucky-Potter diaphragm and grid were not used.

Lithiasis is found most frequently in Wharton's duct, then in Stenson's duct, and then in the submaxillary and parotid glands. The stones are often solitary and small; they are elongated when found in ducts and round if in glands. The opaqueness is variable, and sometimes the stones are radiolucent. In sialography, they will give a lacunar shadow and show changes in the gland canaliculi produced by stones (dilatation and obstruction of ducts, inflammatory processes, or parenchymal atrophy).

Inflammatory processes, such as nonsuppurative acute parotitis, cause dilatation of the ducts and acini, and the oil is located in small drops throughout the gland. The opaque medium stays in the gland for several days.

Mixed tumors cause displacement of the ducts.

Cystic, basilar adenitis and metastatic lymphatic glands of the parotid region may produce an appearance similar to mixed tumors.

Carcinoma produces stenosis of the salivary ducts, an irregular filling defect, or obliteration of the canalicular system. The parenchyma loses its normal structure. The oil may pass in droplike form from the canalicular system to the parenchyma or to the tumor. EUGENE P. PENDERGRASS, M.D.

The Technique of Direct (Percutaneous) Cerebral Angiography. E. Lindgren. *Brit. J. Radiol.*, 1947, 20: 326.

The technique of direct needle puncture or the percutaneous method of injecting radiopaque media into the carotid artery for cerebral angiograms is compared with the open operation method. The former is considered as the procedure of choice and if properly used is adequate and safe.

The opaque media used by the author is umbradil. The concentration is 35 per cent, used routinely on the first injection, and if well tolerated the 50 per cent solution is used on subsequent injections. The 50 per cent solution yields better pictures but is not tolerated by some patients. The amount is 8 or 9 c.c. injected during 2 or 3 seconds.

The puncture is made under 1 per cent novocaine local anesthesia with the patient supine and the head extended backward lying on the cassette changer. The author avoids puncturing the common carotid artery because of the greater dilution of the dye in a greater volume of blood and the confusing overlying shadows of the external carotid distribution. A puncture made as high in the neck as pulsation is felt will strike the internal carotid as a rule and is preferred. Between injections the needle is perfused with physiological saline solution. Some discomfort is produced by injection of the 35 per cent solution as it causes a burning or smarting sensation "inside the eye" for the internal carotid distribution, and pain in the jaws and around the eye for the external carotid distribution. This serves as a guide to the site of the puncture and if the external carotid has been punctured the needle is withdrawn and inserted lower into the common carotid artery. Co-operative patients are warned of this sensation and unco-operative ones are given a general anesthetic, or thorotrast is used.

Once the puncture is made it is desirable not to move the patient to avoid dislodging the needle. Roentgenograms are made in the lateral and anteroposterior projections by an apparatus which will do this without moving of the patient. The first exposure is made during the injection when 3 c.c. are left in the syringe. This shows the arterial system. Two subsequent exposures are made as rapidly as the

cassettes can be changed, showing the capillary and venous systems, respectively. The roentgen tube is adjusted to the other position, a second injection is made, and three more films are exposed as described.

This system was employed in 153 cases and only 4 unsuccessful examinations resulted.

ARTHUR W. PRYDE, M.D.

Planigraphy in the Diagnosis of Bronchogenic Carcinoma. Leo G. Rigler and Thomas B. Merner. *Am. J. Roentg.*, 1947, 58: 267.

Recent publications show that bronchogenic carcinoma is increasing in frequency, both absolutely and in proportion to other types of malignant neoplasms.

Among the various methods used for diagnosis, bronchoscopy occupies first place, especially since it provides a means of biopsy. The poor condition of the patient, however, sometimes prevents its use. In other instances, especially when the carcinoma is localized to the upper lobe bronchi, or when there is a distortion of the bronchi due to extrinsic lesions, bronchoscopy is disappointing.

Great progress has been made lately in the roentgen study of the bronchogenic carcinoma. The diagnostic signs may be the result of secondary manifestations of carcinoma, or of the primary appearance of the lesion.

The secondary manifestations are due to a gradual obstruction of the bronchial lumen by the carcinoma. Westermark described three stages in the development of the obstruction. In the first stage there is diminished air content of the segment of the lung involved because of diminished intra-alveolar pressure and hyperemia. In the second stage, the increasing mass produces a check-valve effect resulting in emphysema. The third stage is characterized by complete obstruction and atelectasis. Fluoroscopy and roentgenograms, taken in the maximum of expiration and inspiration, will help most in demonstrating the various phases of the obstruction.

The primary signs of the carcinoma are a mass either in the hilar region or, less commonly, in the periphery, a localized infiltrative process or a diffuse invasion of the lung. The instillation of iodized oil into the affected bronchi is of definite value in further identifying the process. With the exception of bronchoscopy, it is the most useful method of examination. There are, however, certain contraindications, most important of which are severe dyspnea, fever, toxicity, and uncontrollable cough.

Planigraphy, which is also called tomography or laminagraphy, is a more recent method for the diagnosis of bronchogenic carcinoma. It consists of a body section roentgenography at various depths. A special attachment is used, which permits the film holder and the roentgen tube to move in opposite directions in one plane around a point of rotation which represents the desired depth. A trial exposure is made, usually at about 10 cm. from the table top, with the patient in supine position. Additional films are taken at 8 and 12 cm. from the table top, and so on until the clearest image of the lesion has been obtained. It is also advisable to make a film 1 cm. anterior and another film 1 cm. posterior to the level giving the most information about the lesion. In order to obtain parallel plane films, in some instances it will be necessary to make the exposures in lateral or oblique views in respect to the patient's body.

Important planigraphic signs are the demonstration of an actual defect within the bronchus, the visualization of an irregular elongated stenosis of the bronchus resembling a "rat-tail," and the showing of collateral evidence afforded by the secondary lung changes. For example, a clear cut intrabronchial mass is more indicative of benign adenoma of the bronchus, whereas if there is a rat-tail deformity with surrounding infiltration or atelectasis carcinoma must be suspected.

Planigraphy serves as a supplement to or as a substitute for bronchography. It is not intended, however, to replace the older methods of examination.

The authors used planigraphy in 181 patients suspected of pulmonary disease. Bronchial tumors were found to be present in 47 patients and in 10 of these, a diagnosis of benign adenoma was made. The remaining 37 tumors were bronchial carcinomas, as indicated by the collateral findings. Failures were noted in only 5 cases.

The authors present the planigrams with corresponding diagrams in several illustrative cases. The conclusion is reached that the accuracy of planigraphy compares favorably with other roentgen methods of examination, and if the technique of application continues to improve it may even reduce the importance of some of the methods now in use.

T. LEUCUTIA, M.D.

On Spontaneous Chronic Intestinal Invagination in Adults. P. Bjerre Hansen. *Acta radiol.*, Stockh., 1947, 28: 115.

Although the occurrence of spontaneous intussusception of the intestine has often been described in children, it seldom has been described in adults. Diagnosis, in most instances, has been made by means of a barium enema. However, the author describes 2 cases of intussusception in which the diagnosis was made by means of a contrast enema and barium meal. Although this procedure is not a new one, the author believes it has not been used frequently enough.

Pertinent roentgen findings may be divided into two groups, those visualized by means of a contrast enema and those visualized by means of an oral barium meal.

The enema film reveals:

1. Abrupt, smooth stop of the barium.
2. Bicornate configuration.
3. Partial filling of the invagination sheath in ring shaped stripes, corresponding to the haustra, across the intussusceptum.
4. Filling of the colon but with a central, stripe-like clearing.

Fig. 1. (Hansen). Distinct invagination is seen just at the flexura hepatica combined both with the arched stripes and the filling of the invaginated part of the small intestine produced by administration by mouth.

5. Gaseous dilatation of the terminal ileum.
6. Depression of the hepatic flexure.
7. Elevation of the cecum.
8. Centripetal curving and dilatation of the affected portion of the colon.

The oral barium meal reveals:

1. Delayed flow of the barium through the intestine.
2. Dilatation of the terminal ileum.
3. Beak shaped stricture of the ileum at passage into the cecum, which may be complete, resulting in stenosis or simply as a narrow cord, without peristalsis; the cecum is always found to be displaced superiorly.
4. Partial filling of the arched rings due to retrograde passage.

In adults, the cause for invagination of the intestine is tumor in the majority of instances.

Two cases of intussusception in adults which were diagnosed by means of contrast enema and oral barium are reported. In 1 case the invagination was released after the contrast enema; in the second, it was necessary to resort to surgery.

MAURICE D. SACHS, M.D.

The Roentgenologic Diagnosis of Appendical Calculi. Benjamin Felson and C. Melvin Bernhard. *Radiology*, 1947, 49: 178.

This article is based on 100 cases collected from the literature and 10 personal cases. The latter are briefly described and illustrated with some very unusual roentgenograms. In 9 of the 10 cases the condition was diagnosed from roentgenologic evidence, and in 7 patients, who were operated upon the diagnosis was verified.

A review of the available material established the following facts:

Incidence. Some investigators consider appendical calculi as rare occurrences. On the other hand, Steinert and his coworkers found 10 cases among 104 appendectomies. The authors' 10 cases were noted in an estimated total of 300 appendectomies.

Etiology. There is now fairly good agreement to the effect that appendical calculi are formed, at least in part, *in situ*. According to Kelly and Hurdon, who offer the most plausible theory, if the normal return of the fecal contents from the appendix to the cecum is impaired, inspissation of varying degree occurs. This in turn causes a low grade catarrhal inflammation with its attendant secretion of mucus. Inorganic salts contained in the mucus are precipitated on the surface of the dried fecal particle, the repetition of the process invariably leading to lamination of the calculi. There is an associated appendicitis with an incidence of perforation of almost 50 per cent.

Clinical findings. Of 60 patients whose sex was stated, 47 were males and 13 females. This conforms to the sex ratio observed in acute appendicitis. There are no characteristic clinical symptoms or findings indicative of appendical calculi.

Roentgen findings. The diagnosis is always made on the basis of roentgenologic evidence. When a stone has been demonstrated on a plain film, further identification of its location is made by lateral and stereoscopic anteroposterior roentgenograms, and by gastrointestinal barium studies. In all but 5 cases from the literature the stone was in the right lower quadrant of the abdomen, at the level of the sacroiliac joint or iliac crest. Lamination is a very important diagnostic sign.

Differential diagnosis. This includes urinary calculi, calcified intra-abdominal lymph nodes, gall stones, phleboliths, foreign bodies, nonreticulated bone islands in the ilium, true enteroliths in the bowel, and calcifications in epiploic appendages, cysts, tumors, or ligaments.

Pathology. The involved appendix usually shows a diffuse acute appendicitis with areas of gangrene. Not infrequently, a perforation follows with abscess formation or diffuse peritonitis.

Chemical composition. According to Mayer and Wells, appendical stones consist (by weight) of inorganic material, mostly calcium phosphates (25%), organic residue, mostly vegetable fibers (20%), and substances soluble in fat solvents, soaps, coprosterol, and small amounts of cholesterol (50%).

Treatment. Immediate surgical intervention is indicated in all cases. Of 36 cases in which the outcome was mentioned, 4 terminated fatally and 6 had a stormy course but recovery took place.

T. LEUCUTIA, M.D.

Diagnosis of Ectopic Pregnancy by Hysterosalpingography. Borge Nielsen. *Acta radiol.*, Stockh., 1947, 28: 185.

Hysterosalpingography is infrequently a diagnostic aid in ectopic pregnancy. A 35 per cent water soluble contrast media is used and films are made in varying projections. The rate of media absorption as well as the manner in which the contrast media fills the pregnant tube are observed by serial films.

Pertinent roentgen findings are:

1. Lack of filling of the salpinx and uterine atony
2. Segmental irregularity of the obstructed salpinx
3. Salpinx spasm
4. Nonvisualization of the ovum in the tube.

The author reports the cases of 25 patients on whom hysterosalpingography was done for suspected ectopic pregnancy. Among the first 12 instances, the roentgen findings were positive in 11. In the second group of 13 cases it was desired to rule out ectopic pregnancy, and this was done in 12 of them.

The author believes that the danger of miscarriage is not a contraindication to the procedure. However, the procedure should not be done indiscriminately. This examination is certainly a worthwhile adjunct to the clinician's diagnostic armamentarium.

MAURICE D. SACHS, M.D.

An Epidemic of Inhalation Lead Poisoning with Characteristic Skeletal Changes in the Children Involved. George Cooper, Jr. *Am. J. Roentg.*, 1947, 58: 129.

The clinical picture of various manifestations of plumbism have been described many times since about 300 B.C., when Hippocrates recorded his findings in a case of lead colic in an extractor of metals. Prompt recognition of plumbism in children is more important than in adults, for children react to smaller amounts of lead and more severely. This is true especially of those under 4 years of age. Epidemics of lead poisoning have been reported in which the source of the lead was traced to the use of storage battery casings for fuel. In Staunton, Virginia, there was an epidemic due to this cause. The author discusses the findings in the 19 patients examined. Only 4 patients failed to show abnormal metaphyseal densities on roentgen examination.

The symptomatology in poisoning due to lead inhalation is identical with that due to lead ingestion. The incidence of ingested lead poisoning is highest in spring and summer because the vitamin D producing action of sunlight increases the absorption of ingested lead as well as of calcium. There is no seasonal incidence from inhaled lead. The early symptoms are gastrointestinal—loss of appetite, vomiting, constipation, and abdominal cramps. Persistent and more severe poisoning frequently leads to peripheral neuritis and palsy in adults and occasionally in children. Anemia is a fairly constant finding. Meningoencephalitis is the most serious development. It is frequent in children. The symptoms are persistent projectile vomiting, changes in the victim's mental state (irritability and lethargy), visual disturbances, and alteration of the pulse and respiratory rates. These initial symptoms are followed by delirium, stupor, coma, elevated blood pressure, choked optic discs, convulsions, and separation of the cranial su-

Fig. 1. (Nielsen). A hypermobile uterus which ejected the perabrodil through the fallopian tubes immediately. The pregnant salpinx ends in the shape of a funnel, but it is partly covered with irregular stripes and patches of contrast medium.

Fig. 2. (Nielsen). Same as figure 1, but some time after the injection. The contrast medium is more distinctly visible.

tures. Cortical and optic atrophy are frequent sequelae.

In children the most valuable diagnostic procedure is roentgenographic examination of the skeleton. The x-ray findings are those of homogeneous metaphysical densities. The zones of increased density vary in width up to about 0.5 cm., and vary in density.

The metaphyseal densities are most marked where the bone growth is most active—in the ends of the long bones, at the anterior ends of the ribs, and in the iliac crests. There are several other conditions which produce zones of increased density in the metaphyses. The diagnosis of lead poisoning cannot be made without confirmation from the history and clinical findings. FRANK L. HUSSEY, M.D.

Further Observations on Fracture of the First Rib. B. Roxby Alderson. *Brit. J. Radiol.*, 1947, 20: 345.

The author published, in November, 1944, an article on "Stress Fractures of the First Rib." Various American workers denied the possibility of a spontaneous fracture of the first rib and believed that such an injury could occur only from direct trauma. The author believes that fracture of the first rib does occur frequently from muscular violence, that complete bony union does occur, that nonunion and the formation of a false joint are encountered, that there may be symptoms sufficient to cause the patient to report to his physician, and also that this condition more frequently occurs without sufficient pain to require radiological examination or even to warrant a visit to the doctor.

There is presented a series of case histories of subjects showing the abnormality under review, in one or both first ribs, showing evidence of the fracture, sometimes spontaneous with or without subjective symptoms, sometimes following severe and usually unaccustomed muscular stress, either related to a single episode or more frequently to a particular kind of job, namely, the lifting and carrying of heavy weights.

This academic evidence has been supported by roentgenographs, serial in some cases, demonstrating the healing process, and in some cases complete bony union occurred. In other cases, research into previous roentgenographs or routine 35 mm. fluorographs showed a pre-existing intact rib. The author believes it is probable that spontaneous fracture of the first rib is more common than congenital abnormality. ALFRED O. MILLER, M.D.

The Roentgen Appearance of Primary Reticulum Cell Sarcoma of Bone. Robert S. Sherman and Ruth Evelyn Snyder. *Am. J. Roentg.*, 1947, 58: 291.

Ewing, in 1939, reviewed the classification of bone tumors of the Registry of the American College of Surgeons and accepted reticulum cell sarcoma as a primary bone tumor. Parker and Jackson in the same year published 17 cases of such tumors, 13 collected from the Registry, and 4 of their own. Since then a number of other case reports appeared in the literature.

The authors observed 17 cases of primary reticulum cell sarcoma of bone, all of which were confirmed histopathologically by at least one biopsy.

The literature contains no reference to the value of the roentgen study in reticulum cell sarcoma of bone although often the appearance is quite characteristic. The following factors are of interest:

1. Location in skeletal system. About four-fifths of the tumors involve the tubular bones, 40 per cent boing located in the region of the knee.

2. Location in bone. The tumors may occur in the diaphyseal, metaphyseal or epiphyseal regions so that the location in bone has no particular significance.

3. Site of origin. In the vast majority of cases the tumors arise from the medullary or cancellous bone.

4. Symmetry in bone. This concerns the tubular bones. About one-third of the tumors are symmetrical.

5. Direction of growth. In one-half the cases the growth of the tumor is entirely endosteal; in the other half, with very few exceptions, it is predominantly endosteal.

6. General configuration. An ovoid configuration occurs most frequently, with the fusiform configuration next.

7. Destruction and production in medullary bone. Medullary destruction is a constant and usually predominant feature. Productive changes, i.e., new bone formation, calcification, or osteoid deposition, are observed in about one-half of the cases but they rarely exceed the destructive changes.

8. Structure of the tumor. The structure of the osseous portion is a patchy arrangement of areas of destruction often associated with similar sized areas of production. The periosseous portion has no pattern, there being no calcification in the soft tissue tumor apart from the periosteal reaction.

9. Boundary of the tumor. One of the outstanding features of reticulum cell sarcoma of bone is its ill defined boundary so that it is very difficult to determine the precise extent of the tumor.

10. Condition of the cortex. Cortical destruction is a constant finding, but no expansion or marked thickening of the cortex is present.

11. Condition of periosteum. Periosteal change is not a prominent feature although some periosteal reaction is found on careful study in about two-thirds of the cases. Usually this is of the lamellated type, and often accompanied with a minute periosteal triangle at one margin of the tumor.

12. Periosseous changes. The majority of the tumors have a periosseous extension but this rarely exceeds the size of the area within the bone.

13. Joint changes. Involvement of the joint, especially around the knee, is not uncommon. Synovitis occurs frequently but the effusion is never great.

14. Pathological fracture. If the destruction is very pronounced pathological fracture may result. Most fractures heal following radiation therapy.

15. Multiplicity. There is never involvement of more than one bone.

16. Rate of growth. The duration of symptoms for an average of 6½ months as well as the roentgen findings of periodical check-up examinations suggest that reticulum cell sarcoma is a rather actively growing tumor.

17. Response to irradiation. The immediate response is very satisfactory. The periosseous mass disappears first, followed by re-establishment of the cortex, subsidence of the periosteal change and, finally, by reossification of the destroyed area, the density being slightly greater than in the normal bone. The late results, likewise, are very encouraging. In the authors' series, 5 patients are well 5 years or more after treatment, 5 patients are well 3 years after treatment, 3 died, and the remainder were treated more recently.

The differential diagnosis of reticulum cell sarcoma of bone from osteogenic sarcoma of medullary origin is often difficult. The most important distinguishing signs are the radioresistance of the osteogenic sarcoma in contrast to the reticulum cell sarcoma and the lack of reparative changes following roentgen therapy. Other conditions that have to be considered in the differential diagnosis are Ewing's tumor, metastatic cancer in bone, osteomyelitis, tuberculosis, neuroblastoma, and lymphoblastoma.

The case histories of all 17 patients are presented and their respective roentgenograms reproduced for the purpose of illustration.

The conclusion is reached that reticulum cell sarcoma of bone is relatively benign, and runs a long course with not infrequent 5 year survivals. Irradiation constitutes the sole method of treatment and there is some evidence that it may be a radiocurable tumor. T. LEUCUTIA, M.D.

Roentgen Diagnosis of Pigmented Villonodular Synovitis and Synovial Sarcoma of the Knee Joint. Raymond W. Lewis. *Radiology*, 1947, 49: 26.

In 1941 Jaffe, Lichtenstein, and Sutro grouped, under the name of pigmented villonodular synovitis of the knee joint, lesions formerly described in the literature under a wide variety of designations, such as chronic hemorrhagic villous synovitis, giant cell fibrohemangioma, fibrohemosideric sarcoma, sarcoma fusigigantocellulare, benign polymorphocellular tumor of the synovial membrane, xanthoma, xanthogranuloma, giant cell tumor, and myeloplaxoma. They distinguished between a circumscribed and diffuse form of villonodular synovitis and considered the condition as inflammatory rather than neoplastic.

In the present preliminary report the author deals with the diffuse villonodular synovitis, since the circumscribed lesions are seldom demonstrated roentgenographically. His experience extends to 4 surgically proved cases, which are described in the text, and 7 cases studied only by clinical and roentgenographic means.

The general roentgen characteristics of the diffuse villonodular synovitis and the diffuse intracapsular tumors of the knee joint, of which synovial sarcoma (synovioma) is the most common, are often identical. They are as follows: bones of a young adult, monarticular involvement, excessive amount of synovial tissue which may appear smooth in outline and homogeneous in density or nodular in outline and of varying density, normal joint spacing with no indication of cartilage involvement, and complete absence of osteoporosis or atrophy of the leg.

Clinically, as a rule, there is a long history of swelling of the knee extending from one to several years, no known etiology, relatively little discomfort or disability, no fever, and a normal or somewhat increased sedimentation rate.

Although, as mentioned above, diffuse villonodular synovitis and synovial sarcoma of the knee joint are frequently identical in their roentgen appearance, the author found 3 criteria which may permit a differentiation: (1) if the nodular soft tissue masses are in part or wholly outside of the joint capsule, the lesion is not villonodular synovitis, but may be synovial sarcoma, fibrosarcoma, or some other condition; (2) if the lobulated soft tissue masses in or near the joint contain scattered or irregular deposits of amorphous lime, the lesion is almost certainly a synovial sarcoma; and (3) if the lesion of the soft tissues of the joint has invaded bone, the condition is probably synovial sarcoma.

In the 4 cases described in the text the treatment consisted of one or several synovectomies. However, the results were so disappointing that in the more recent cases roentgen therapy is being tried. Some good results from roentgen therapy in villonodular synovitis are described in the literature.

In view of the importance, from the point of view of treatment, of establishing a differential diagnosis between villonodular synovitis and synovial sarcoma, exploratory operation and biopsy would seem definitely indicated in every case.

The article is illustrated with typical roentgenograms and drawings showing the salient points.

T. LEUCUTIA, M.D.

Panroentgen Therapy from the Clinical, Technical, and Biological Point of View (La panröntgenterapia dal punto di vista biologico tecnico e clinico). **Arduino Ratti.** *Radiol. med.*, Milano, 1947, 32: 206.

The author, in a lengthy article, considered it proper to make an examination of the biological, technical, and clinical problems involved in panroentgen therapy (total irradiation of the body with therapeutic roentgen rays) to see how and when much more extended use might be justified. He traces the origin of the idea (submitting the whole body contemporaneously to the therapeutic action of roentgen rays) to the beginnings of the radiological era, its advancement proposed by Dessauer (1905), and the first clinical applications by Teschendorf (1927), Dale (1928), and Sgalitzer (1932). He believes the term

"telepanroentgen therapy" to be the most preferable, in contrast to various other terms such as teleroentgen therapy (total), panirradiation, telepanirradiation, and panroentgen therapy.

BIOLOGICAL AND TECHNICAL FUNDAMENTALS

The fundamental characteristic of panroentgen therapy is the simultaneous irradiation of the whole body in such a way that no cell belonging either to the fixed organs or systems or the mobile systems (blood) escapes the action of the radiations. The effects of irradiation are not immediate but manifest themselves after a certain time lag, according to the technical characteristics of the irradiations and the diverse species of tissues and cells. As a consequence, from the biological point of view one can also consider the irradiation of large fields in brief successions of time as total and simultaneous irradiation. From the physical standpoint a technique so executed is less exact because of the possibility that in the border zone of the two fields there may be areas of over exposure and some without exposure, and from the biological point of view the computation of the quantity of radiation received by the cells of the mobile tissues is less precise; but from the practical clinical point of view irradiation conducted in this manner can offer considerable advantages. As the condition of simultaneity need not be absolute, so also the condition of totality can be applied less exactly; for instance, the head or lower members may be excluded from the irradiation. While it is necessaryto make a distinction between these types of irradiation from the technical point of view, the results obtained are not much different, provided that the parts excluded do not assume relevant dimensions which would prohibit subtotal irradiation. The author then considers the list of principal technical factors of irradiation in detail—the target distance, the quality of the rays used, the quantity of the rays (singularly and totally), and the manner of distribution in time and space.

CLINICAL APPLICATIONS

The author considers the use of panroentgen therapy in the vast field of therapeutics and its principal indications. It is used for two large classes of disease: (1) systemic and generalized disease and (2) local disease. Among the former are certain dermatoses (eczema, psoriasis, urticaria), various diseases of the hemolymphatic system and reticulohistiocytic system (especially the leukemias and erythemias), and generalized secondary metastatic tumors. With regard to the dermatological conditions its use has been limited and the author prefers to resort to other forms of therapy; however, he considers its use is more appropriate for various diseases of the hemolymphopoietic system and for generalized secondary metastases of tumors. He states that leukemias, in general, act the same as malignant neoplasms before roentgen therapy is given.

The author then discusses the therapeutic effect of irradiation and explains it on the basis of a greater sensitivity of the pathological elements— essentially immature elements. This is the classical concept upon which the radiotherapy of malignant neoplasms was founded. The author then discusses the problem of dosage, contrasting that for the common method of local irradiation with that for general total irradiation. Clinical experience in the latter field has not been very vast. Regarding panroentgen therapy in leukemia he states that from the biological point of view it has been shown that quantities of irradiation, though small, are capable of determining the regression, albeit temporary, of the clinical and hematological picture of leukemia. He then brings forth 2 hypotheses explaining this fact and discusses both—a direct and indirect action—without taking one position categorically.

He considers the factor of radiosensitivity and presents the fact noted by him and others, of a notable sensitivity of the red blood cell elements and white blood corpuscles which necessitates suspension of the total irradiation therapy of leukemia and erythremia (Vagnez) because of the onset of a definite anemia which jeopardizes a successful result. This concept of a notable sensitivity of the red blood cells and white blood cells demonstrates that there is an insufficient "safety factor" or interval between the respective sensitivities which interferes with obtaining the therapeutic objective. This demonstrates that panroentgen therapy is the only method of irradiation which permits an idea of the degree of radiosensitivity of the hemolymphatic system and that for the time being this value is to be considered more correct.

The author then notes that the results of panroentgen therapy with regard to the effects on the fixed tissues, as contrasted with those of local irradiation, have not created much interest because the irradiations have been made with exceedingly small doses. He believes that panroentgen therapy is of value as a method for the study of the radiosensitivity of the hemolymphopoietic system. For the sake of completeness he discusses the insurgence of the artificial menopause and the appearance of the phenomenon of "irradiation sickness."

SUMMARY

After a detailed explanation, the author expounds the biological and technical principles upon which is founded the total irradiation of the body with roentgen rays (panroentgen therapy) and passes to the technical aspects, by which it is sought to resolve the problem of its practical application. Although the therapeutic irradiations executed with this modality affect all the cells and all the tissues of the body contemporaneously, the concepts of radiosensitivity and the criteria of dosage, as well as of the therapeutic effects and dangers, from the experiences with ordinary roentgen therapy, do not apply. The author then analyzes the results which were obtained in the treatment of hemolymphopoietic system diseases, of malignant lymphogranuloma, and of generalized malignant tumors, concluding that the most fertile

field for the use of panroentgen therapy is that of the chronic hemopathies, especially the not advanced forms. The results in the cases of malignant lymphogranuloma were nearly all negative and in the cases of generalized malignant neoplasms the results were questionable. G. Albin Liva, M.D.

Irradiation of Experimental Cerebral Tumors. Experimental Production of Brain Tumors in Mice. Katharine Tansley. *Radiology*, 1947, 49: 62.

In the first part of this article Tansley deals with the experimental production of brain tumors in mice. After a detailed review of the literature, the author describes the method used by herself. Benzpyrene and methylcholanthrene powders have been used. The latter has proved much more successful, 24 sarcomas and 10 gliomas having been obtained in 77 animals. Two strains of mice were used, the albino Ni strain, originally obtained from the National Institute for Medical Research, London, and a mixed pigmented stock of uncertain origin bred in her own laboratory. Because of experimental difficulties only 1 glioma was preserved for transplantation. This now has been successfully transmitted to 103 mice of the Ni strain.

The operation for implanting the carcinogen into the brain tissue was performed when the mice were 2 days old. The glioma used for grafting was obtained from an animal 397 days after the implantation of methylcholanthrene. The operation for the implantation into the brain of the glioma grafts was likewise performed when the mice were 2 days old. Grafts of glioma tissue were successful in every animal that survived the operation. The macroscopic and microscopic appearances of the induced tumors and the grafted gliomas are discussed in detail, several photomicrographs being used for the purpose of illustration. In general, the grafted gliomas resembled the cerebral tumor described by Lopez in a rat and said by him to be similar to a human glioblastoma isomorphe. The tumor cells invaded the brain, particularly through the perivascular and ventricular spaces; they also penetrated the true brain tissue without producing any visible reaction or round cell infiltration.

In the second part of the article, Tansley and Wilson give their observations on the effect of roentgen irradiation on the grafted gliomas, 39 of the 85 grafted mice having been subjected to this procedure. The treatment was carried out with 180 kv. (Villard circuit), 0.5 mm. of copper plus 1.0 mm. of aluminum, which gave a high value layer of 0.95 mm. of copper, at a distance of 25 cm. and a dose rate of 154 roentgens per minute. The experimental arrangement is described and illustrated with diagrams.

Total doses of from 1,623 to 3,247 roentgens were administered. The effect of irradiation on the growth of the tumor varied greatly. In general, the higher doses were more effective in arresting the growth, but in no case was the tumor entirely destroyed. Five animals died during or within a few hours of the exposure, all showing profuse hemorrhages from the tumor tissue. Other animals were examined from 7 to 18 days after irradiation, and were found to exhibit widespread necrosis and diffuse bleeding in the tumor tissue. T. Leucutia, M.D.

The Treatment of Recurrences and Evaluation of Criteria for the Selection of Treatment of Cancer of the Larynx. John V. Blady. *Am. J. Roentg.*, 1947, 58: 331.

There are three well established methods for the treatment of cancer of the larynx: laryngofissure, laryngectomy, and irradiation.

The purpose of the present study is to review the recurrences that developed at the Temple Univer-

Criterion	Recommended Treatment
1. *Metastases*	
a. Cervical metastases present	Irradiation to primary lesion Irradiation and/or surgery and/or radon
b. Cervical metastases absent	1. Laryngofissure 2. Laryngectomy 3. Irradiation
2. *Histopathology*	
a. Squamous cell carcinoma, Grade 1 and 2	1. Laryngofissure 2. Laryngectomy 3. Irradiation
b. Squamous cell carcinoma, Grade 3	1. Laryngofissure 2. Laryngectomy
c. Squamous cell carcinoma, Grade 4	1. Irradiation 2. In early cases limited to 3a, 3b, 3c, laryngofissure may be indicated
3. *Extent of Involvement*	
a. Growth limited to one cord not invading arytenoid or posterior commissure	Laryngofissure
b. Growth limited to anterior commissure and anterior third of each cord	1. Laryngofissure 2. Irradiation
c. Growth involving one cord, ventricle	Laryngofissure
d. Subglottic extension	Laryngectomy
e. Growth involving anterior commissure, cord and base of epiglottis	Laryngectomy
f. Growth involving cord, aryepiglottic fold with limitation of motility	1. Irradiation 2. Laryngectomy
g. Growth involving posterior commissure, pyriform sinus, aryepiglottic fold and epiglottis, or party wall	1. Irradiation
4. *Motility and Mobility*	
a. Impaired motility of cord	1. Irradiation 2. Laryngectomy
b. Partial impairment of mobility of larynx	1. Laryngectomy 2. Irradiation
c. One side of larynx fixed or greatly impaired	Laryngectomy
5. *General Factors*	
a. Presence of other disease contraindicating radical surgery	1. Irradiation 2. Laryngofissure
b. Temperament of patient—if patient cannot become adjusted to laryngectomy	Irradiation

sity Hospital, Philadelphia, following the use of the three methods, and to establish proper criteria for the selection of subsequent treatment.

Recurrences after laryngofissure. The reported cures for this method are 80 to 85 per cent. At the Chevalier Jackson Bronchoscopic Clinic of Temple University Hospital, 71 laryngofissures were performed during the period between 1930 and 1937. There were 10 recurrences (17%). Only 4 of these received additional treatment, 3 patients being well at present (2 following roentgen irradiation and 1 following laryngectomy).

Recurrences after irradiation. A series of 81 patients were treated by roentgen irradiation between 1931 and 1941 inclusive. Of these, 56 were classified as intrinsic, and 25 as extrinsic. In the intrinsic group there were 13 recurrences (23%), and in the extrinsic group, 6 recurrences (24%). An analysis of the 19 recurrences reveals that 14 patients received additional treatment, 5 patients having survived for 5 or more years (4 of these following a second course of intensive roentgen irradiation and 1 following laryngectomy).

Recurrences after laryngectomy. The recurrence rate for laryngectomy is 24 per cent. Fifteen patients with recurrences after laryngectomy were subsequently treated by intensive roentgen irradiation. All died, the average survival time being only 9½ months. Repetition of the surgery and interstitial radon implantation remained equally unsatisfactory.

The author stresses the importance of the proper selection of the three methods under various circumstances. The suggested criteria of selection are arranged in the accompanying table.

T. Leucutia, M.D.

Soft Tissue Changes in Early Acute Osteomyelitis. George J. Baylin and John C. Glenn, Jr. *Am. J. Roentg.*, 1947, 58: 142.

The authors report roentgenographic changes manifest in the soft parts surrounding the involved bones which at times are present within a matter of a few hours after the onset of bone infection.

The most consistent change in early active osteomyelitis is a roughening of the normally sharp line of demarcation between the subcutaneous shadow and the muscle bundles. Concomitant with this change is another important abnormality, namely, the tendency toward obliteration of the intermuscular cleavage planes. The usual normal subject will show a very clear-cut change roentgenographically at the muscle-subcutaneous line, but within 24 hours after the onset of acute osteomyelitis there is regularly present considerable distortion at this stripe, characterized chiefly by transverse irregular lines of increased density extending from the muscle borders into the subcutaneous shadows. These lines are not particularly straight or regular in length or width, but seem to produce a crisscross pattern which suggests that they may be vascular and lymphatic channels that have become patent or dilated. Apparently, a similar change occurs in the usually clear-cut intermuscular planes which normally stand out as lines of decreased density, for in most cases of early acute osteomyelitis it is very difficult to separate the muscle compartments.

The changes described are obviously not of the same degree in every case. The most important fact concerning the changes under discussion is that the early soft part abnormalities extend only as far as the bone is involved. The changes do not pass beyond the joints unless the joints themselves are involved. These changes should be differentiated from those occurring in acute sprains, tumors, blood dyscrasias with extravasation, and edema of varied origins. The changes discussed have been manifested primarily in children, yet on several occasions they have been noted in adults.

Frank L. Hussey, M.D.

MISCELLANEOUS

Biological Studies in the Tolerance Range. Egon Lorenz, W. E. Heston, Allen B. Eschenbrenner, and Margaret K. Deringer. *Radiology*, 1947, 49: 274.

The biological effects of chronic whole-body irradiation from gamma rays were studied by the authors in mice, rabbits, and guinea pigs with daily doses of roentgens, as follows: 8.8, 4.4, 2.2, 1.1, and .11 given in 8 or 24 hours per day for periods of as long as 3 years, with total doses (in some instances) as high as 5,900 roentgens for mice, 6,000 roentgens for guinea pigs, and 12,000 roentgens for rabbits. The purpose of the studies was to provide experimental data from which conclusions might be drawn regarding the probable tolerance dose in the human.

Curves of the mortality rates in the different groups indicate that the destructive action of radiation is cumulative even for such small doses as .11 roentgens given in 8 hours per day. The blood-forming organs of rabbits and mice were found to be extremely resistant to the effects of chronic irradiation, and the peripheral blood picture shows little change except in those animals in which leukemia develops. In guinea pigs, on the other hand, the effects of radiation upon the hematopoietic system is pronounced, and results in death from anemia and thrombocytopenia. Up to the present time, no deaths from this syndrome have resulted in the animals at the 1.1 and .11 roentgen level.

The most important findings in these experiments have to do with the carcinogenic action of long continued radiation. The majority of the tumors occurred in mice and the most important of these were leukemia, lung tumors, ovarian tumors, and tumors of the mammary gland. Tumors of these same types, with the exception of mammary tumors, were also observed in the nonirradiated controls. For the most part, chronic irradiation did not appear to significantly affect the over-all incidence of cancer, but altered only the time at which the tumors appear, indicating a dependence upon dose rate. In the case of ovarian tumors, however, there was a considerably

higher as well as earlier incidence in mice following doses as low as .11 roentgens per day when compared to the controls.

Histological studies as well as breeding experiments showed that radiation injury to the ovary of the mouse is irreversible and cumulative. Radiation injury to the testes of mice and guinea pigs, on the other hand, is reversible and cumulative only to a certain degree. No conclusive evidence for the production of genetic changes was obtained in studies on mice exposed continuously up to six generations to 1.1 roentgens per day after fertilization of the ova took place.

The following conclusions were drawn by the authors from their experimental results. The blood picture is of little value in determining radiation damage, except in the case of obvious overexposure. The carcinogenic action and sterility effects dominate the picture of radiation injury. The present permissible dose of .1 roentgen per day in the human should be maintained. Due to the considerably higher as well as earlier incidence of ovarian tumors in mice following cumulative doses of .11 roentgens per day, when compared to that in the controls, the permissible dose should be reduced for women to perhaps .02 roentgens per day, or their time of exposure should be reduced to a few years. Since there was no evident radiation injury to the skin of experimental animals exposed to 8.8 roentgens given in 8 hours per day to a total dose up to 10,000 roentgens, a permissible dose to the hands of 1 roentgen per day might be considered safe if the rest of the body does not receive more than .1 roentgen per day.

J. H. Freed, M.D.

The Hematological Effects of Ionizing Radiations in the Tolerance Range. Leon O. Jacobson and E. K. Marks. *Radiology*, 1947, 49: 286.

The authors report the effect of continued whole body irradiation from gamma rays on the hematopoietic system of mice, rabbits, and guinea pigs with daily doses of 8.8, 4.4, 2.2, 1.1, and 0.1 roentgens given in 8 or 24 hours per day for periods as long as 3 years. This work was done in conjunction with controlled studies of the peripheral blood of personnel exposed or potentially exposed to radiations during work performed on the Plutonium Project.

From the results of these studies, the authors conclude that a lymphocyte reduction in the peripheral blood is the most sensitive indicator of acute or subacute exposure to externally originating ionizing radiation or internally deposited radioisotopes. No hematological change was detectable in the peripheral blood in mice, rabbits, or guinea pigs with a daily whole body exposure to 0.1 roentgen gamma radiation extending over 3 years. In some of the mice, however, ovarian tumors developed after continued exposures of 0.1 roentgen per day even though no peripheral blood changes were noted. All three species of animals exposed to doses of 2.2, 4.4, or 8.8 roentgens showed definite hematological changes of significance after varying lengths of time. The guinea pig is the most sensitive, the mouse intermediate, and the rabbit most resistant so far as hematological changes produced by radiations are concerned.

In studies on the personnel of the Plutonium Project no hematological changes were found which were referable to radiation exposure in the "tolerance range." The results of this experimental work, however, indicate that studies of the hematological constituents of peripheral blood are not reliable for determining possible incipient damage from radiation exposure in the "tolerance range," and therefore other clinically applicable tests are urgently needed.

J. H. Freed, M.D.

The Tolerance Dose and the Prevention of Injuries Caused by Ionizing Radiations. Rolf M. Sievert. *Brit. J. Radiol.*, 1947, 20: 306.

The risks of radiation injuries have been steadily increasing during the past 25 years because of the use of increasing intensities of x-radiation and greater quantities of radioactive substances, and because of wider use in such fields as research, teaching, and engineering, where medical knowledge is often lacking and where their administration is in the hands of personnel not familiar with their biological effects. The possible use of atomic energy in the future will further greatly increase the problem of protection against injuries by ionizing radiations and it is probable that it will become a general social problem of prime importance.

In considering protection against radiation, interest is concentrated on the effects of the ionizing rays on three parts of the human organism: the skin, the blood and blood forming tissues, and the sex glands and germ cells. The so-called safe tolerance dose is of fundamental importance in all work concerning the prevention of radiation injuries. From previous studies, the safe skin tolerance dose may be fixed at between 0.1 and 0.5 roentgens per day. In determining the blood tolerance dose the term "integral dose" introduced by Mayneord in 1940 is of importance because it gives a measure of the total energy absorbed by the body. It will be of great value for assessing the risks due to high energy protons and neutrons of which the safe tolerance dose may be much smaller than that recommended for x-rays and gamma rays because of their greater biological effect in many cases for the same tissue ionization. Studies correlating the blood changes with radiation risks in the use of x-rays and gamma rays have shown that in all probability radiation quantities as low as from .02 to .05 roentgens per day can give rise to blood changes after a comparatively short time. The genetic tolerance dose appears to be of the order of magnitude of .01 roentgen per day. Hence, the author believes that a safety tolerance of .01 roentgen per day should not, if possible, be exceeded.

The prevention of injuries caused by ionizing radiation is mainly a question of organization. In Sweden, supervision of establishments using x-rays and

radioactive substances is now required by law, and such supervisory work is carried out largely by the Institute of Radio-Physics. Every person wishing to be employed in radiological work is obliged to undergo a periodic medical examination. A 6 week holiday has been established for all x-ray workers, periodic inspections are made of all establishments using x-ray or radioactive substances, and recommendations for protection are made and enforced. Such control work is organized in combination with research and teaching.

Propaganda and instruction appear to be the most important measures for preventing radiation injuries according to the author. A careful and satisfactory working technique is clearly the most important protective measure. Such a system of regulatory control seems desirable and will undoubtedly be adapted by other countries with the advent of the new atomic age. JOHN H. FREED, M.D.

Effects of Total Surface Beta Irradiation. John R. Raper. *Radiology*, 1947, 49: 314.

Because of superficial absorption, irradiation with beta rays in doses below the acute lethal range results in greater gross and superficial damage than that following irradiation with x-rays or gamma rays. The lesions produced are inflammation and swelling of the eyes, epilation, dryness of the skin, and ulceration of the skin.

It was found that the larger the animal, the greater the dose required. Total surface beta irradiation exerts an acute lethal action in each species at a characteristic dosage, but the main wave of mortality occurs later than that noted following irradiation with x-rays. The median lethal dose (LD 50) for each species varied from baby rats at 2,200 r.e.p. (roentgens equivalent physical) to rabbits at 17,000 r.e.p.

Studies indicate that beta rays, a strictly superficially absorbed radiation, bring about their lethal action by a total mass or volume effect while gamma rays, which irradiate all elements of the body more or less uniformly, do not.

A series of experiments showed that the greatest recovery was in the first 3 days following sublethal irradiation, and within 8 days complete recovery is obtained. Following this there is a period of over-compensation for which no obvious explanation is found.

Blood studies show no direct effect on the cellular constituents of the peripheral blood.

JOHN O. LAFFERTY, M.D.

Experiments on the Mechanism of the Biological Action of Fast Neutrons. J. S. Mitchell. *Brit. J. Radiol.*, 1947, 20: 368.

The author has made a quantitative comparison of fast neutrons with mean energy between 4 and 4.5 mev. from a polonium-beryllium source and radium gamma radiation, using the summation method for lethal effects in adult male mice. The experiments were performed chiefly to determine whether the relevant mechanisms of the biological action of fast neutrons are identical with or differ from those of gamma radiation and whether the effects of the two radiations are completely additive. Determinations were also made of the relative biological efficiency of the two radiations for unit energy absorption with different overall exposure times.

The contributions to the tissue dose from the fast neutrons and the accompanying gamma radiation were determined by measurement of the absorption of the ionization in lead by means of small ionization chambers with walls of graphite and of a carbon-polystyrene mixture. One roentgen of fast neutrons is defined as the dose which produces the same energy absorption per unit volume of tissue as that produced by 1 roentgen of the usual filtered gamma radiation of radium of mean energy, approximately 0.8 mev.

Two series of biological summation experiments were carried out, the first involving 24 individual experiments with a mean overall time of exposure of 24 hours and the second, 38 individual experiments with a mean overall exposure time of 48 hours. The "mixed" radiations applied consecutively in different orders were mainly one-third dose contributions of one type of radiation and two-thirds dose of the other, and vice versa, but 50 per cent mixtures were also used in the second series.

In both series of experiments, statistically significant departures from additivity were found, following the deaths in from 0 to 20 days after exposure. The "mixed" radiations consecutively applied were found to have less lethal effect than comparable doses of either fast neutrons or gamma radiation alone. This result indicates a difference in the mechanism of the biological action of these two radiations. The author explains this difference in the mechanism of biological action of fast neutrons and gamma rays as probably being due to a difference in the time of action on the cells. Proliferating cells are most sensitive to gamma radiation during a short interval in the prophase stage of mitosis. It is likely that, on account of the high specific ionization of the recoil protons, the proliferating cells exhibit a much more uniform sensitivity to neutrons through both the "resting" stage and mitosis, so that because of the length of the former, the main effect of fast neutrons will be shown by resting cells. With regard to tolerance problems, it is believed that the effects of fast neutrons and gamma radiation should, nevertheless, be regarded as additive from the practical standpoint.

The relative biological efficiency of fast neutrons in terms of the efficiency of the gamma radiation was found in the experiments with a mean exposure time of 48 hours to have the value of 32.0 ± 8.6, which is significantly higher than the value for short exposure times. The author believes that this finding indicates that the lethal effects of gamma radiation on normal mammalian cells are produced at least in part by chromosome interchanges.

JOHN H. FREED, M.D.

Discussion on Radiotherapy in the Treatment of Nonmalignant Superficial Eye Lesions. R. Affleck Greeves, B. W. Windeyer, M. Lederman, N. S. Finzi, and Others. *Proc. R. Soc. M.*, Lond., 1947, 40: 570.

R. Affleck Greeves deals solely with the treatment of superficial corneal lesions by means of mild suberythematous radiotherapeutic doses. Eighteen years ago he began treating corneal lesions which occurred in connection with cases of acne rosacea keratitis. Improvement was noted. The eyes whitened, infiltrates were replaced by healing scars, and pain and photophobia vanished. He states that radiotherapy does not cure the disease. Exacerbations which are especially prone to occur in spring and early summer can be checked in most cases by means of radiotherapy if this treatment is instituted early. Radiotherapy has proved to be markedly beneficial in recurrent abrasions and superficial punctate keratitis. In these cases the ulceration is usually limited to the corneal epithelial layer and heals without leaving any scar. In some cases attacks may continue in a moderate form after a course of treatment. After a suitable interval, treatment may be required. About one-half of the patients with superficial punctate keratitis who have been treated have been benefited. Only in obstinate cases of phlyctenular keratitis has it been found necessary to use radiotherapy. In mild cases of spring catarrh when eyelids are normal during the winter months and show fresh manifestations in the early part of each year, treatment is indicated. Treatment should be immediate in cases of recurrence. In treatment of other types of corneal ulcer, including Mooren's ulcer and dendritic ulcer, and any form of deep keratitis, radiotherapy has not been successful. B. W. WINDEYER states that the cardinal principle in radiotherapy of malignant disease of the eye is to avoid or shield the eye itself whenever possible, because of the danger of permanent damage from even moderate dosage. The most common sequelae are those associated with the eyelids and the lacrimal apparatus, the conjunctiva, and the lens. Scarring of the lids may cause entropion or ectropion, and closure of the punctum by scar tissue may result in persistent epiphora. Heavy irradiation of the conjunctiva may by followed by chronic conjunctivitis with some loss of sensitivity and chronic irritability. In such cases vascular changes are usually apparent. Microscopically, there is degeneration of the arterial vascular endothelium, followed by regenerative hyperplasia with narrowing of the lumen of the vessels, and clinically, there is dilatation of the superficial capillaries with permanent telangiectasis. Degeneration of the lens with cataract formation may occur. Typical irradiation cataract is posterior cortical with radiating rows of vacuoles and these may be arrested in the vacuolar stage or may go on to maturity, vacuolar opacities gradually becoming scattered through the entire lens cortex, which eventually becomes completely opaque. A mature irradiation cataract shows no special clinical features and responds as well to operative treatment as do other forms of cataract. The technique used at the Middlesex Hospital has been irradiation of the cornea from the lateral and from the medial sides, with a beam which is sharply defined by means of a lead glass applicator with a 2 to 5 cm. diameter aperture. The patient is treated with the eye open and fixated in one position. A dose of 100 roentgens measured at the aperture of the applicator is delivered to each field. The estimated dose received by the cornea is a total between 120 and 130 roentgens per treatment. This dose is repeated at fortnightly intervals up to 4 treatments per series. This treatment may be repeated. The treatment of cases of acne rosacea keratitis gives the most gratifying results. Recurrent erosion and abrasion respond with rapidity but may recur. Superficial punctate keratitis of the multiple erosion type has shown satisfactory response in one-half of the cases. The results of treating spring catarrh have been disappointing.

M. LEDERMAN states that radiotherapy has not yet received the recognition it merits by ophthalmologists. The reasons for this are twofold: (1) current misconceptions concerning the susceptibility of the eye to radiation damage and (2) the eye diseases for which radiotherapy is suitable are not common, hence its field of usefulness is rather restricted. The view that the eye is readily damaged by radiation cannot now be supported, as it is largely based on early, unscientific experimental work, and the ocular disasters encountered by pioneer radiotherapists. Damage to the eye is avoidable in the treatment of nonmalignant lesions, but the risk of ocular damage has to be accepted in the treatment of malignant neoplasms which affect the eye or its neighboring structures. Radiation with beta and gamma rays and x-rays can be used; each have their own indications. Hemangioma keloids, solitary papillomas, and hyperkeratosis are benefited by radiation therapy. For inflammatory lesions it is less satisfactory and should not be used without additional consideration. In superficial punctate keratitis and rosacea keratitis x-ray radiation is of value. An initial dose between 10 and 15 roentgens is used, which is gradually increased to from 40 or 50 roentgens per treatment twice weekly until a total dose from 200 to 250 roentgens has been given. Individualization of the treatment is advisable. Corneal ulceration and recurrent erosion are favorably influenced by radiotherapy. Mooren's ulcer presents a special problem. The results of treatment are variable.

A. J. DURDEN SMITH states that Mooren's ulcers are treated by contact radiation with unscreened radium applicators. As a rule 3 treatments at intervals of 6 weeks are given. The dosage of the radium applicators used is of full strength, i.e., 5 mgm. per square centimeter, and is substantially unscreened—the contact surface consisting of 0·1 mm. of monel metal. The most usual sizes are 1·0 and 1·25 cm. in diameter. The typical applicator gives 6,000 roentgens on the surface. The treatment time is short. Forty ulcers were treated. Eighteen of these healed

and presented no recurrence for periods of 2 years or more. Seventeen lesions were bilateral on arrival. Of these, 7 healed on both sides as a result of treatment. Four healed on one of the sides but not on the other and the remaining 6 failed to heal on either side.

N. S. FINZI said that it was necessary to point out that gamma radiation would not fall off in anything like the same degree per millimeter of tissue as the beta radiation, in that Durden Smith has stated that he gave 6,000 roentgens of the beta radiation.

EUGENE WOLFF said that he had seen half a dozen cases of stenosis of the punctum and canaliculus after radiation.

B. THORNE-THORNE asked if radium or x-ray application would bring about relief in a case of dermolipoma of both eyes.

WINDEYER felt confident that the dosage which he had described had been given. He did not think that splitting of the canaliculus would correct scarring of the punctum (Wolff). He thought a dermolipoma would quite unlikely be radiosensitive (Thorne-Thorne).

M. LEDERMAN, in referring to the dosage used in the treatment of Mooren's ulcer, had not used a consistent dose. FRANK L. HUSSEY, M.D.

Radium Therapy of Hemangioendothelioma of the Uterine Cervix. Harry H. Bowing, Robert E. Fricke, and James T. McClellan. *Am. J. Roentg.*, 1947, 57: 653.

The authors report 4 cases in which a hemangioendothelioma occurred in or on the cervix. Of the 4 patients, 2 are dead, but their death cannot be attributed directly to the neoplasm of the cervix. Two of the neoplasms occurred in unmarried women and 2 in multiparous women. The youngest patient was 39 years of age, the oldest, 62. The most prominent symptom was bleeding. In those patients in whom menstruation still occurred there seemed to be a prolongation of the menstrual periods with increase in the amount of blood at the periods. Vaginal discharge was not a prominent symptom, even when the vaginal vault was filled by the tumor. The tumors seemed very radiosensitive, which usually is true of tumors of endothelial origin.

MISCELLANEOUS

CLINICAL ENTITIES—GENERAL PHYSIOLOGICAL CONDITIONS

Sequelae of Atomic Bomb Explosion. George V. LeRoy. *J. Am. M. Ass.*, 1947, 134: 1143.

Army and Navy medical missions studied the results of the explosions of the atomic bombs in Hiroshima and Nagasaki, Japan. The two most impressive features of the investigation were the tremendous toll of casualties and the syndrome due to large amounts of gamma radiation. One-sixth of the casualties were crushed under buildings or were trapped in burning buildings, and died instantly from the direct heat of the bomb. About one-seventh of the casualties showed no injury on the day of the explosion, but received sufficient gamma rays to become sick 1 to 5 weeks later. By rough estimate, about 85,000 persons in Hiroshima and 50,000 persons in Nagasaki required medical care on the day of bombing. The types of injuries that required treatment resulted from the characteristic products of the bomb, which are (1) mechanical energy "blast," (2) heat, (3) light, and (4) ionizing radiation. These injuries could be classified as wounds, 70 per cent, burns 65 to 85 per cent, and radiation, more than 30 per cent.

It was impossible to estimate the amount of radiation that any one person received. However, it is certain that the intensity of the gamma rays varied with the distance from the bomb by the law of the inverse square, and it is also evident that heavy buildings and underground shelters gave more protection than wooden structures and open space.

Those who received the largest amount of radiation developed fever and diarrhea the next day, purpura in 4 to 7 days, and then rapidly failed and died. Autopsy findings were those of purpura hemorrhagica with petechiae, gastrointestinal erosion, and disappearance of normal lymphocytes and marrow cells.

Most patients developed symptoms between 7 and 28 days after the bombing, and this syndrome consisted of epilation, intractable diarrhea, purpura, fever, leukopenia, and anemia. The complications were those found in agranulocytic angina. The loss of hair was rarely complete and in most patients it began to grow again in 2 or 3 months. Leukopenia was the outstanding laboratory finding, and recovery was rare when the total count dropped below 600 per cubic millimeter. It is estimated that the mortality in this group was between 50 and 75 per cent.

The least severe form of this syndrome appeared from 3 to 5 weeks after bombing and consisted of weakness, malaise, diarrhea, and mild inflammation of the mouth and throat. Some patients developed epilation. Anemia was constant and often progressive. There was mild leukopenia and thrombocytopenia. The bone marrow was badly damaged but in most cases showed some evidence of regeneration within 7 to 10 days after injury. Spermatozoa were absent from the tubules of the testes in the majority of the men who received enough radiation to cause symptoms.

The therapy of patients with radiation injury should be directed to (1) maintain fluid and electrolyte balance, (2) control infection, (3) combat hemorrhagic tendency, and (4) combat anemia.

ROBERT MAYO TENERY, M.D.

Melkersson's Syndrome: A Report of 5 Cases, with Special Reference to the Pathologic Observations. Karsten Kettel. *Arch. Otolar.*, Chic., 1947, 46: 341.

Melkersson's syndrome is a characteristic facies morbi comprising the following triad: chronic swelling of the face, peripheral facial palsy, and lingua plicata. As a rule, the disease begins in childhood or youth with an attack of peripheral facial palsy, which may be bilateral and may show a tendency to relapse. Either simultaneously or later (sometimes not until several years later) a swelling of the face occurs, which is especially localized to the lips. The tongue is distinctly furrowed (lingua plicata). The syndrome is characteristic. In the acute stage the disease has been mistaken for erysipelas; in the chronic stage it has been mistaken for acromegaly. Both clinically and pathologicoanatomically the facial palsy shows a close correspondence to Bell's palsy.

In fresh cases the patient should be observed for about 2 months; if there are no signs of beginning mobility after that period, decompression of the facial nerve should be performed in accordance with the Ballance-Duel method. Moreover, the same treatment is indicated if the spontaneous mobility has ceased before complete restitution has been obtained, and in case of relapsing palsy.

The author presumes that the vasomotor fibers of the face follow a shorter or longer course in or along the facial nerve. Paralysis of the sympathetic fibers involves both paresis of the vascular supply of the facial nerve, resulting in facial palsy and paresis of the vessels of the face, followed by edema.

C. FRED GOERINGER, M.D.

A Plastic Operative Procedure for the Repair of Large Circular and Elliptical Body Surface Defects. Boyan Hadjistamoff. *Plast. Reconstr. Surg.*, 1947, 2: 362.

Large circular or elliptical body surface defects are formed chiefly after the removal of malignant tumors, excision of old atonic wound surfaces, and function-hindering scars. After certain injuries there also occurs extensive circular loss of substance which may require normal skin covering.

In the majority of cases the easily performed Thiersch-Reverdin graft may be done. In other

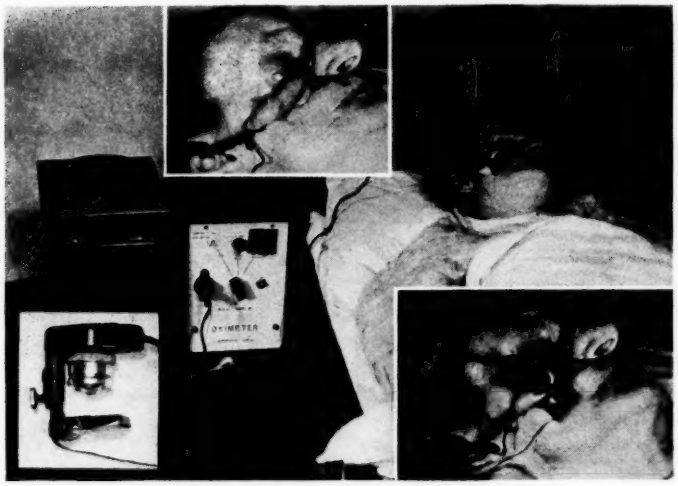

Fig. 1 (Douglas and Millikan)

cases, owing to scarred, poorly vascularized wounds, special functional requirements, or to the danger of new contracture, the closure must be effected with normal skin.

The closure of the wound, which is accomplished at one sitting through skin flap shifting, is more natural, quicker, and less painful.

The author describes a procedure for closing large circular or elliptical defects in which he utilizes neighboring skin and distributes the repair task.

Considering the local blood supply, two skin flaps are made, a quadrangular (EABCD=a) and a triangular (TAB=b) flap. Two incisions are required, an oblique one (AB), and an incision running more or less parallel to the edge of the defect. The oblique incision (AB) amounts approximately to the radius length of the circular defect. The width of the flap (a) should be about one-half to two-thirds of the width of the defect. The flaps are mobilized and pulled over the defect. There still remains three uncovered areas which are easily closed by mobilizing the adjacent skin edges.

This procedure has been successfully applied to three regions of the body—upper shoulder, upper back, and ischial and trochanter regions.

LOUIS T. BYARS, M.D.

The Blood Circulation in Pedicle Flaps. Preliminary Studies on a Photo-Electric Test for Determining Its Efficiency. Beverly Douglas and Glenn A. Millikan. *Plast. Reconstr. Surg.*, 1947, 2: 348.

The present test, in which the authors employ an apparatus developed during the war for measuring continuously the oxygen saturation of arterial blood in man, represents a method of determining the viability of tube flaps. The adequacy of circulation is estimated from the speed with which blood enters the flap following the release of a tourniquet. The blood content of the flap is measured photoelectrically by a simple modification of an oximeter ear unit. The present method measures only changes in the total amount of blood in the flap. It cannot distinguish between the efficiency of arterial supply and venous drainage. The rapid return of blood to a previously "milked" flap after releasing the tourniquet indicates a good arterial supply but tells us nothing about adequacy of venous drainage. Decreased blood content following release of the tourniquet indicates efficient venous drainage.

The oximeter ear unit consists of a U-shaped structure bearing a small incandescent lamp on one leg, and a photocell assembly on the other.

For the present experiment, the unit has been modified to fit on flaps of different thicknesses without any alteration in blood circulation.

Upon releasing the tourniquet around one end of the previously "milked" flap, while the other is left on, blood enters the flap and the resultant flushing reduces the transmission of light. This change can be followed continuously by the lamp on one side of the flap, and the photocell on the other.

A typical test consists of applying tourniquets at each end of the tube. The circulation is cut off by tightening the tourniquet at one end; the flap is then pressed free of blood. Without allowing a return of circulation, the other tourniquet is tightened and the oximeter adjusted. The pressure of the tourniquet at one end is then quickly removed, and readings are taken at 5 second intervals for 2 or 3 minutes.

The oximeter test offers a very rapid method of testing the efficiency of pedicle flaps. Predictions of

successful transfer based on the test have been justified in all 8 cases in which it has been applied. Since flaps may safely be transferred as soon as the oximeter test gives evidence of adequate circulation, considerable time may be saved between operations. Preliminary experiments indicate that the photoelectric method can also be applied to the study of metabolic as well as circulatory changes in pedicle flaps, and in small extremities.

LOUIS T. BYARS, M.D.

SURGICAL PATHOLOGY AND DIAGNOSIS

Fluid Blood in Doubly Ligated Vascular Segments as a Result of Thrombolysis (Fluessiges Blut durch Thrombolyse in doppelt unterbundenen Gefaess-strecken). **M. Zehnder.** *Helvet. chir. acta*, 1947, 14: 162.

Two theories have been advanced to explain the presence of fluid blood within ligated vascular segments. According to one theory, there is an inhibition or breakdown of coagulating substances as in carbon monoxide poisoning and asphyxia. The other explanation as confirmed by the present experiments is thrombolysis or autolytic fibrinolysis. The Baumgarten experiment of double ligation of the parts of such vessels as the vena cava, jugular vein, saphenous vein, and common carotid artery was repeated in rabbits, horses, and sheep, the condition of the stagnant blood between the ligatures being examined at different intervals with modern coagulation tests. In early specimens, taken after 3 days, a firm, gelatinous coagulum was found, while later specimens consisted of fluid blood. This fluid blood did not coagulate spontaneously nor after the addition of thrombin. A complete lack of fibrinogen substances was demonstrated. Addition of hemophilic blood containing fibrinogen caused instantaneous coagulation. The number of blood platelets in the fluid blood was also diminished, and in later specimens the blood platelets had disappeared altogether. It is suggested that the blood platelets and fibrin having been used up in the coagulation process, the fluid blood within doubly ligated vascular segments must be liquefied, autolyzed, or thrombolyzed blood.

Analogous conditions were demonstrated clinically in a case of subdural hematoma containing fluid blood. An increased fibrinolytic titer was demonstrated in the circulating blood of a patient with hematomas of the soft tissues. It is therefore probable that local autolysis of the coagulum is associated with a general fibrinolytic reaction in the blood.

The author stresses the significance of local autolysis or thrombolysis in bland thrombosis, i.e., phlebothrombosis as compared with thrombophlebitis, in venous claudication due to exertion thrombosis of the axillary veins and secondary hemorrhage following traumatic thrombotic vascular occlusion. One might explain in a similar manner the secondary hemorrhage in traumatic rupture of the spleen and the intermittent paralysis of cranial nerves following basal fracture, as being due to autolytic changes in thrombi and coagula. Liquefaction of subdural hematomas occurs in a similar manner.

The increase of fibrinolytic power in the circulating blood following the occurrence of hematomas might also explain the effect of autogenous and foreign blood injections on the consolidation of pneumonia (fibrinous coagulation within the pulmonary alveoli).

EDITH SCHANCHE MOORE.

EXPERIMENTAL SURGERY

Vascular Reactions during Experimental Hemorrhage. Nervous and Humoral Factors of Posthemorrhagic Peripheral Vasoconstriction in the Dog (Sur les réactions vasculaires au cours de l'hémorragie expérimentale. Les facteurs nerveux et humoraux de la vasoconstriction périphérique posthémorragique chez le chien). **Leon Binet and M. Burstein.** *Rev. hémat.*, 1947, 2: 168.

As the result of a new perfusion technique, the authors have been able to study the tonus of the peripheral vessels in experimental hemorrhage. The decrease in the blood mass, even in cases in which the resulting hypotension is very slight, produces an intense peripheral vasoconstriction. This reaction is essentially of central origin and conditioned by the increase in tonus of the vasoconstrictor centers; however, during the hemorrhage the blood acquires vasoconstrictor properties, probably because of a discharge of adrenalin. The vasoconstriction is immediate; it is weak in those animals which stand the bleeding poorly and very marked in the opposite types. It is suppressed by section of the 4 inhibiting nerves. The degree of anesthesia of the animal also plays a part. The vasoconstriction may be absent after a massive or very sudden hemorrhage. In such a case partial restitution of the blood mass may allow vascular reactions of adaptation to enter into play.

The posthemorrhagic vasoconstriction may disappear because of exhaustion of the centers or following ischemia. It is easy to depress the tonus of the vasoconstrictor centers which are stimulated by hypotension.

Increasing the blood mass acts in the opposite direction and causes a peripheral vasodilatation.

RICHARD KEMEL, M.D.

Intravenously Administered Gelatin—A Toxicity Study. Milton J. Vander Brook, Stanley C. Lyster, Boyd E. Graham, Noel E. Pomeroy, and George F. Cartland. *J. Lab. Clin. M.*, 1947, 32: 1115.

A highly purified 5 per cent gelatin solution, prepared especially for intravenous therapy in human beings, was well tolerated by dogs when given repeatedly for several weeks in amounts commensurate with the fluid lost by hemorrhage.

The only morphological pathology which might be attributable to gelatin in this series of experiments was the presence or increase of sudanophile droplets in the Kupfer cells. The significance of such a change is not known. The function of the Kupfer cells was

apparently not altered. None of the dogs developed infection of the respiratory tract or at the sites of bleeding and infusion.

Only the sedimentation rate was altered by gelatin. This phenomenon is common to all macromolecular substances, and occurs also when plasma protein concentrations are elevated. Gelatin does not interfere with the formation of hemoglobin or plasma protein, both of which are partially depleted by hemorrhage, when infused weekly for periods of as long as 3 months.

Gelatin does not appear to be stored in the liver or kidneys. A major portion is excreted by the kidneys. The fate of the balance is unknown.

SAMUEL KAHN, M.D.

Experimental Production of Ulcers in Closed Gastric Pouches in Dogs. I. F. Stein, Jr., M. I. Grossman, and A. C. Ivy. *Surgery*, 1947, 22: 552.

The authors attempted to elucidate the role which acid pepsin plays in ulcer production and to ascertain if continuous exposure of gastric mucosa to normal gastric juice would result in ulcer formation. For this purpose they utilized healthy mongrel dogs weighing from 25 to 35 pounds.

In the first group of 5 dogs a portion of the greater curvature of the stomach, comprising one-third to one-half of the fundus, was resected according to the Heidenhain technique, but the resected segment was completely sutured into a closed pouch. A clamp was used for the remaining gastric portion.

In the second group of 8 dogs, a two-stage procedure was employed, the first being the construction of the usual Heidenhain pouch. After from 9 to 18 days, the dog was reoperated upon, and the stoma of the Heidenhain pouch was tightly sutured in 2 layers, thus creating a closed gastric pouch.

In the third group of 6 dogs, primary closure was established, as in Group 1, following which an avascular region of the middle or inferior end of the pouch was attached to the parietal peritoneum underlying the second left nipple which was used as a point of localization. Twenty-four hours later, a 15-gauge needle was inserted through the abdominal wall into the pouch, a pressure determination was made with a water manometer, and gastric juice was collected to relieve pressure and also for titration. Late readings were made every 12 to 24 hours.

All 5 dogs in the first group died in 2 to 5 days of acute ulcer formation with perforation and peritonitis.

Four of the 8 dogs in the second group died of acute ulcers with peritonitis in 3 to 8 days following closure of the stoma. One dog, which was sacrificed 20 days after closure of the stoma, showed a greatly distended pouch without pathologic changes. The remaining 3 dogs died of recurrent causes without ulcer.

Four of the 6 dogs in the third group died in 7 to 12 days of acute ulcer of the pouch with perforation and acute peritonitis. The remaining 2 dogs died in 13 and 14 days from extraneous causes without pathologic changes in the pouch. All the animals with an average free acid concentration of over 40 milliequivalents per liter had acute ulcer of the pouch with perforation.

In the majority of cases, acute ulcers with perforation develop in closed Heidenhain gastric pouches. Clinically, conditions approaching those encountered in a closed pouch are found in pyloric stenosis; the increased pressure and increased secretory activity often present in this condition may predispose to extension of perforation of an ulcer.

ROBERT TURELL, M.D.